An observational trial to study the role of Thromboelastography in comparison with conventional coagulation testing to assess the disease severity among adult patients with snake envenomation at a tertiary care centre hospital in Southern India.

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE M.D. BRANCH I (GENERAL MEDICINE) EXAMINATION OF THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI TO BE HELD IN APRIL 2015

DECLARATION CERTIFICATE

This is to declare that the dissertation titled "**An observational trial to study the role of Thromboelastography in comparison with conventional coagulation testing to assess the disease severity among adult patients with snake envenomation at a tertiary care centre hospital in Southern India.**" is my own work, done under the guidance of Dr. Samuel George Hansdak, Professor and Head, Department of Medicine IV, submitted in partial fulfilment of the rules and regulations for the MD Branch I – General Medicine Degree Examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, to be held in April 2015.

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BONAFIDE CERTIFICATE

This is to certify that the dissertation titled **'An observational trial to study the role of Thromboelastography in comparison with conventional coagulation testing in assessing the disease severity among adult patients with snake envenomation at a tertiary care centre hospital in Southern India.'** is the bonafide original work of **Dr. Perla Harsha Teja,** in fulfilment of the rules and regulations for the M.D., Branch I, General Medicine Degree Examination of The Tamil Nadu Dr. M.G.R. University, Chennai to be held in 2015.

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Sub: **FLUID Research grant project:**
An observational trial to study the role of thromboelastography (TEG) in snake envenomation in adults.
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Dear Dr. Harsha Teja Perla,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

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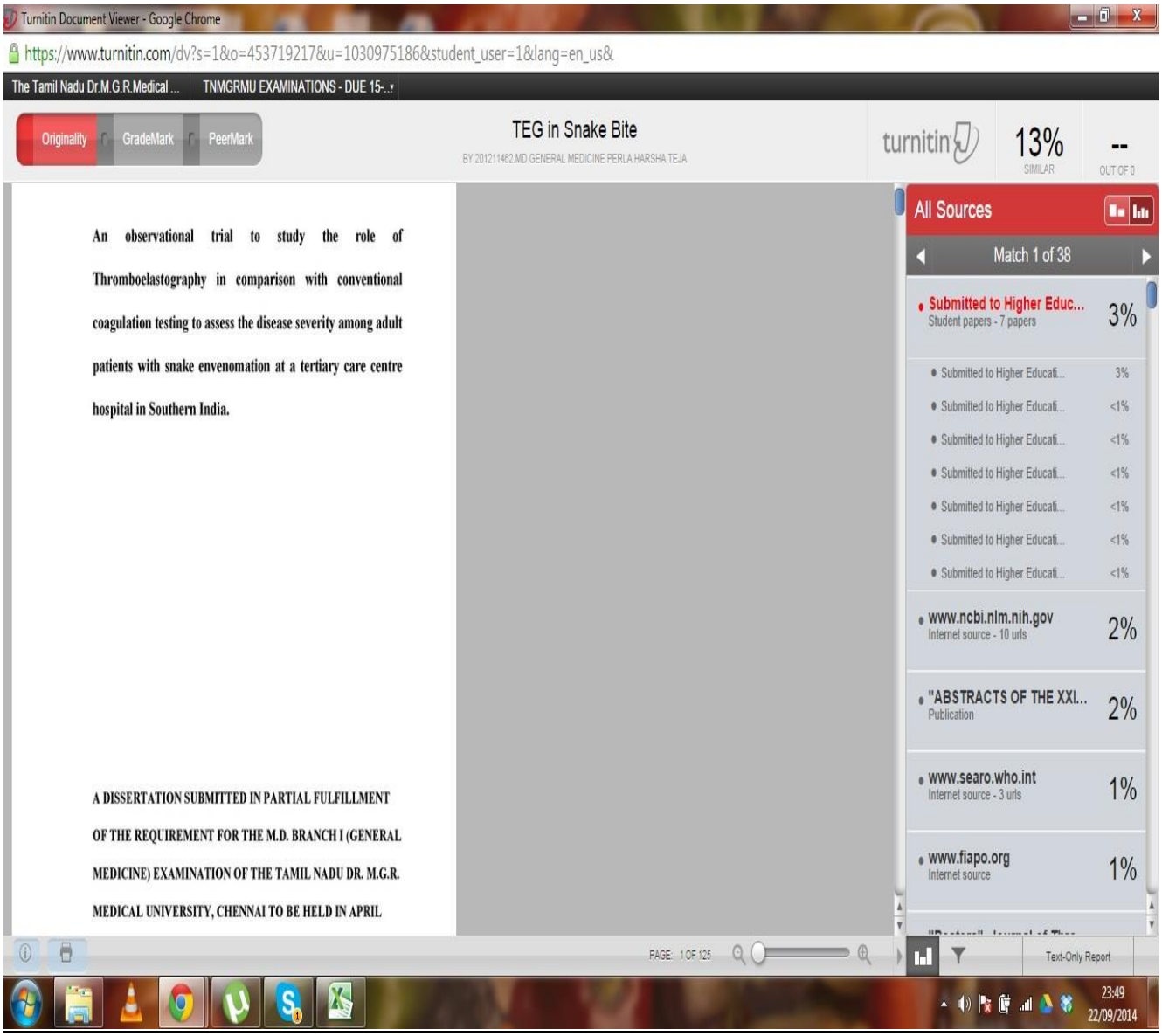

ACKNOWLEDGEMENTS:

- First and foremost I thank the Lord Almighty for His constant presence and guidance at every step of my thesis work.
- I would like to thank both my guide, Dr Samuel G Hansdak and my co guide Dr Sukesh C Nair for their patience, immense support, suggestions, valuable guidance, help and constant encouragement throughout my work on this dissertation.
- I would like to thank Dr Abhilash KPP, Dr Moses Kirubaraj and all the junior doctors and staff in the Emergency Medicine department for their cooperation while patients were being enrolled in their department.
- I would like to thank entire senior staff of the Department of Clinical Pathology especially Ms Jennifer and Ms Ramya for their cooperation in helping me to process the laboratory samples for coagulation studies.
- I am also grateful to the entire Department of Internal Medicine for all the support I received in preparing this dissertation and throughout my three year course in Internal Medicine.
- I am deeply indebted to the patients I have recruited, for their time and willingness to be a part of the study. At this point I would like to thank all my patients who agreed to participate in this study for their whole hearted co-operation.
- I thank all my colleagues for their help and support.
- I would also like to thank Mr. Janaki Raman from the Department of Clinical Epidemiology and Biostatistics for helping me with the statistical analysis of my data.
- I specially thank my wife, parents and my sister for their invaluable and constant support.

ABBREVIATIONS

ARF: Acute renal failure

ASV: Anti Snake Venom

APTT: Activated Partial Thromboplastin Time

BT - Bleeding time

CMCH: Christian Medical College and Hospital

CO2: Carbon Dioxide

CT - Clotting time

DIC - Disseminated intravascular coagulation

ECG – Electrocardiogram

EEG: Electroencephalogram

FDPs: Fibrin degradation products

FFP: Fresh frozen plasma

Hb: Hemoglobin

HMV: High Molecular Weight Kininogen

ICU: Intensive Care Unit

IV: Intravenous

JIPMER: Jawaharlal Institute of Postgraduate Medical Education and Research

LDH - Lactate dehydrogenase

MA: Maximal Amplitude

PGIMER: Post Graduate Institute of Medical Education and Research

PT: Prothrombin time

RBC: Red blood cell

ROTEM: Rotational thromboelastometry

RVV: Russell's Viper Venom

SEARO: South East Asia Regional Office

SIRS: Systemic Inflammatory Response Syndrome

STROBE: Strengthening The Reporting of Observational Studies in Epidemiology

TEG: Thromboelastography

USA: United States of America

USSR: Union of Soviet Socialist Republics

VICC: Venom Induced Consumptive Coagulopathy

WHO - World Health Organisation

WHO/SEARO: World Health Organisation South East Asia Regional Office

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ABSTRACT

TITLE OF THE ABSTRACT: 'An observational trial to study the role of Thromboelastography in comparison with conventional coagulation testing in assessing the disease severity among adult patients with snake envenomation at a tertiary care centre hospital in Southern India.'

DEPARTMENT: General Medicine

NAME OF THE CANDIDATE: Dr.Perla Harsha Teja

DEGREE AND SUBJECT: M.D. Branch I General Medicine

NAME OF THE GUIDE: Dr Samuel George Hansdak

Objectives: To compare Thromboelastography with conventional coagulation tests in patients presenting with snake envenomation.To analyse the demographic, clinical and laboratory profiles; to identify the predictors of severe envenomation.

Methods: In this prospective observational cohort study with internal comparison, patients with snake envenomation presenting to CMC Hospital, Vellore between January 2013 and June 2014 fulfilling inclusion criteria were divided into low and high severity groups. Demographic, clinical and laboratory parameters were collected and analysed. We compared the two groups with respect to thromboelastography and conventional coagulation tests in identifying severe envenomation and clinical evidence of coagulopathy at admission. Correlation of thromboelastography with factors casuing coagulopathy and the risk factors

that would predict severe envenomation were also analysed. Statistical analysis was done using STATA 13 software.

Results: A total of 72 patients were included: 32 with mild envenomation and 40 with severe envenomation. Sensitivities of thromboelastography (TEG), whole blood clotting time (WBCT), prothrombin time (PT) in identification of severe envenomation were 92%, 56% and 64%. Sensitivities of TEG, WBCT andPT in identification of clinical coagulopathy were 81.3%, 59.4% and 65.6%. The predictive value for a milder course when TEG was normal was 88.95% compared to WBCT and PT (56%, 62.5%). TEG was also highly sensitive in identification of thrombocytopenia (94.7%, p value: 0.0001). None of the risk factors analysed were found to be statistically significant on multivariate analysis in predicting severe envenomation.

Conclusion: In patients with an acquired cause of coagulopathy such as snake envenomation, thromboelastography as a single test could prove to be a significant advance in the better and early identification of severe envenomation and coagulopathy.

Keywords: Snake bite, Envenomation, Thromboelastography, Coagulopathy.

INTRODUCTION

Snake envenomation is a common medical emergency that is seen predominantly in rural areas. Snake envenomation often leads to significant mortality and morbidity if adequate supportive and treatment measures are not initiated early. Hence snake envenomation's and the resultant deaths are a major and important public health problem in the rural tropics. This is particularly due the fact that health services in these areas are not only poorly accessible but are often suboptimal, and, in some instances, have a scarcity of antivenom, which is the only specific treatment. India not only has the highest number of envenoming's annually but also has the highest mortality rate annually with an estimated 11,000 deaths occurring every year according to current estimates.(1)

Traditionally snake envenoming is still managed using routine tests like 20 min whole blood clotting time (WBCT) and prothrombin time, which form the basis for administration of Anti Snake Venom (ASV) to the patients. Therefore it is important to accurately know the coagulation status of the patients at admission for effective administration of ASV. Thromboelastography (TEG) is a relatively new technique that assesses the dynamic coagulation status of the blood. Management algorithms based on Thromboelastography for conditions like liver transplantation, massive trauma and cardiac surgery have been shown to decrease both transfusion requirements and intraoperative blood loss. The purpose of the study is to describe the clinico-epidemiological profile of patients with snake bite, role of thromboelastography as a predictor of snake envenoming and to assess the clinical severity in patients with snake envenoming. Hence it can be assessed in future for better management of patients with snake envenomation.

Vellore district and its nearby areas are heavily infested with venomous snakes, and the victims are mostly healthy young individuals mostly belonging to the lower socio-economic strata, most of them bread winners of the family.

This is a prospective observational cohort study done on patients presenting with newly diagnosed snake envenomation to Christian Medical College and Hospital (CMCH), Vellore. All patients fulfilling the inclusion criteria were assessed by a clinical research form at admission to casualty in CMCH. Routine blood investigations were done as per protocol and blood samples for Thromboelastography were collected along with the routine investigations. The patients were followed up till discharge or death to assess the final outcome. Further analysis of TEG parameters against various coagulation parameters was studied and analysed.

AIMS AND OBJECTIVES

Aim:

The primary aim of the study was to study the role of Thromboelastography (TEG) in assessing the disease severity among adult patients with snake envenomation in a tertiary level teaching hospital in South India.

Objectives:

The objectives of the study were:

1. To prospectively study the demographic characteristics, details of clinical and laboratory parameters among adult patients admitted with snake envenomation to a tertiary care center, Christian Medical College and Hospital, Vellore.

2. To study in detail the demographic, clinical and laboratory risk factors predicting high disease severity in patients with snake envenomation.

3. To compare Thromboelastography with conventional coagulation assays (20 minute whole blood clotting time, Prothrombin time, activated partial thromboplastin time) in assessing the disease severity in patients with snake envenoming.

REVIEW OF LITERATURE

The complex inter-relationship between Man and Snake is filled with ignorance and prejudice. In this scientific era, we should learn to respect the creatures by studying them.

Ramona and Desmond Morris: *Men and Snakes (1965).*

Snake bite is an important neglected tropical health disease which has a high socio -economic impact on the community especially in the rural areas. It can be classified as an important occupational hazard in many parts of the world, especially in countries with predominant rural population working in the fields such as India. In developed countries such as America and Europe there is higher frequency of snake bites amongst the people who are in the habit of keeping snakes as their pets, many of the times it being unlawful. In developing countries snake bites which are dangerous occur mainly especially among rural population who are active as various agricultural workers, daily wage labourers, cattle and goat herders and rarely fisherman. Other significant population group affected are the people of certain tribes such as *Irula* in South India who act the traditional and native snake charmers.(2)

HISTORY OF SNAKE BITE:

Snakes have always evoked a feeling of awe and curiosity. Their apparent renewal of life with casting of skin and the power of some of them to inflict suffering and death have given them a supernatural aura which made them worthy of worship by some ethnic groups. Knowledge regarding snakes and the effects of envenomation

dates back to centuries. Even primitive men knew that snakes can cause diseases. There are wonderful tales of famous snakes like “Vasuki” and “Thakshaka” of Indian mythology. In one Homeric epic, the wound of Philoctetes was said to be caused by snakebite. The snake sacred to Asclepius, the Greek god, lives in clefts of earth and can heal wounds and ulcers by licking them. In ancient Egypt magical religious treatment was given by snakebite.

The earliest scientifically documented reference to Indian snakes available might be credited to Dr. Patrick Russell. He was responsible for distinguishing many venomous snakes from non-venomous ones. He had written about and investigated many snakes. His work was extensive particularly on viper it was thus named Viper Russelli, appropriately named after him.(2)Sir J. D. Fayrer (1873) carried out detailed investigation on the physiology of venom of Indian snakes and wrote a book titled “Thantoophidia of India” in 1874. Col. Frank Walls (1908) strived hard to add our knowledge of the habits and distribution of snakes in his work entitled “The Poisonous Terrestrial Snakes of our British Indian Dominions and How to recognize them”**.** It was Col. Gharpurey (1935), medical man turned ophiologist, who first attempted to dispel the ignorance and superstition woven around the Indian snakes, both venomous and non-venomous. He wrote book called “Snakes of India” in semi technical knowledge**.**

The most important landmark in the treatment of snake envenomation was the development of anti-snake venom which was prepared by Calmette. Monovalent antivenom was first developed against Russell’s viper in India. Later came the polyvalent antivenom from the central research institute, Kasauli. The Later developments were supportive measures like dialysis and blood component therapy. Latest trends are rapid immunodiagnostics and administration of specific monovalent

anti-venom, development of antivenin against locally seen snakes and development of vaccine.

PROBLEM OF SNAKE BITE:

The actual true worldwide burden of snake bite is not well known and documented because of high level of under reporting and serious misreporting.

Worldwide burden of snake bite with emphasis on South East Asia:

Swaroop and Grab in 1954 were the first to assess the global incidence and mortality of snake bites.(3) Their study published in the bulletin of the World Health Organization estimated 500,000 envenomings and 30,000 – 40,000 deaths per year (data from China, USSR and central European countries was unavailable at that time). As they lacked relevant information, these figures by Swaroop and Grab are certainly an underestimation of the true burden of the problem.

The second assessment by Chippaux JP et al again published in the bulletin of the World Health Organization (WHO) in 1998, reported that there are about 5 million snakebites worldwide each year, leading to 125,000 deaths.(4) This study was more reliable as it was based on a greater number of publications. Still many information gaps remained in the study, one of the main question being how much were the local studies representative of the wider epidemiological situation.(4)According to Chippaux, Myanmar had the highest number of deaths secondary to snake bite among all the Asian countries. The majority of the bites involved the Russell's viper, which constituted about 70% of the total bites.

According to this study, in India the data regarding incidence and mortality are fragmentary because less than 40% of snake bite patients attend hospitals for medical care rather first consults traditional practitioners or quacks and only subsequently resort to modern medicine. **Most of the data regarding the epidemiology of snake bite are very unreliable due to the poor condition of the reporting systems in place in developing countries. Moreover, the mortality and morbidity secondary to snake bite are a gross underestimation as most of the bites (approximately 80% of all documented cases) occur among non-urban/rural population.**(4)

Kasturiratne et al conducted a study in 2007 which was based on the WHO database. The study concluded that at least 4,21,000 snake envenomation's and 20,000 deaths occur from snake bites globally every year.(1)The primary data was obtained by the researchers by three ways namely searching for snake bite publications, extraction of country-specific mortality data from databases maintained by United Nations organizations, and identification of grey literature by discussion with key informants. This study also warns that the actual figures might be as high as 94,000 deaths and 18,41,000 envenomation's globally every year. That study also concluded that approximately one case of snake envenomation occurs for every four cases of snake bite. Based on aforementioned fact, they predicted that the worldwide incidence could be anywhere from 1.2 million to 5.5 million every year. South Asia was estimated to have the highest number of cases of envenomation's (approx. 1,21,000). This number was closely followed by South East Asia region (1,11,000) and Eastern Sub-Saharan African region (43,000) yearly. The study concluded that with 81,000 envenoming's and 11,000 deaths annually India to have highest number of envenoming's in the

world. Among the Asian countries, Sri Lanka (30,000 bites per year), Vietnam (30,000 bites per year) and Nepal (20,000 bites per year) were the other countries apart from India to have a very high incidence of envenoming's.(1)

A postal survey conducted in 21 of the 65 administrative districts of Bangladesh estimated an annual incidence of 4.3 per 100,000 population and a case fatality of 20%.(5)

A recent review article by Alirol et al in 2010 again stresses the fact that South Asian region was the hot spot for snake bites and India being the country with the maximum burden.(6)

Indian scenario – Snake bite in India:

Haiti *et al* in 1992 conducted an epidemiological survey of snake bites among 26 villages of Burdwan district, West Bengal and showed an annual incidence of 0.16 per cent per year and mortality rate of 0.016 per cent per year.(7) They also showed that the number of bites were maximum at the onset of monsoon period in the months of July and August. They also showed that the majority of the patients went to the traditional healers or consulted them prior to coming to the hospital.(7)

Kulkarni ML & Anees S (1994)(8)conducted eight years prospective study on Pediatric victims up to 18 years of age in a teaching hospital from 1985 to 1992 in Karnataka. Males were predominant over females with male to female ratio of 2:1. Most of the victims 40.4% belonged to 11-15 yrs. Maximum (33%) bites occurred between October to December followed by 31.4% between April to June. Majority 90% of victims were from rural area and 79.9% bites were on the lower limbs. 58.6% victims had hemotoxic envenomation and 12.5% cases had neurotoxic envenomation.

Mortality recorded was5.2%.(8)

Lal P et al. (2001)(9)carried out a seven years retrospective descriptive study to know the Socio-demographic profile of snake bite cases admitted to JIPMER Hospital, Pondicherry from 1990 to1996. A proportional increase in incidence of snake bite was observed from 2.9/1000 admissions in 1990 to 5.2/1000 admissions in 1996.Adults of 15-60 yrs age group accounted 81.8% of cases and male to female ratio was 2.1:1. Majority(68%) were rural males and 93.8% of cases were agricultural workers/ labourers. 40% of bites occurred during rainy season. Mean duration of hospital stay was 2 days. Majority85% were relieved or cured and 13.5% mortality was recorded.(9)

Bawaskar H S (2002)(10)conducted a three years prospective study of snake bitecases admitted to Bawaskar Hospital and Research Centre, Mahad , Raigad, Maharashtrafrom January 1998 to January 2001. Most 29.7% of victims were less than 20 yrs followed by 25.3% belonged to 21-30 yrs age group. Most 65.9% of bite occurred during monsoon season. Of the 91 cases, 46 (50.5%) were envenomated of which 43.5% showed haemotoxic symptoms and 56.5% showed neuroparalysis. Mortality of 10.9% was recorded and all were due to neurotoxic envenomation.(10)

Chauhan S et al (2005) (11)conducted a five years retrospective study with aim of studying pre-hospital treatment received by snake bite victims admitted to PGIMER Hospital, Chandigarh from January 1997 to December 2001. First aid was given in 70.8%of cases prior to hospitalization, of which 41.4% received first aid from Quacks. 12.7% of victims directly went to PGIMER Hospital. ASV was given in 41.4%, tourniquet in22.86%, Incision and drainage in 20%, Tetanus toxoid in 7.14% and local remedies in5.7% of cases. 43.2% victims needed mechanical ventilation and 6.95 days was the average duration of Hospital stay.(11)

Brunda G& Sasidhar RB (2007)(12)conducted a five years retrospective study from 1999 to 2003 in University College of Science, Osmania University, Hyderabad. They observed that majority of the cases 71% belonged to 21 to 50yrs age group. Males76% were predominant over females with male to female ratio of 3:1. Most of the bites50% were recorded in rainy season during June to September.(12)

Bawaskar H S et al. (2008)(13)conducted one year prospective study of snake bite victims admitted to five hospital of five different districts of rural Maharashtra. 26.9%victims belonged to 21-30 yrs age group followed by 19.2% victims in 11-20 yrs age group. 48.4% of bites occurred between June to October. 60.4% victims had bites on lower limbs. Maximum 90 (49.5%) bites occurred between 6 AM to 6 PM and 75% of bites that occurred during this time period were by viper species and all the 45 cases that occurred between 12.01 AM to 6AM were due to elapid species. 71.9% of victims had fang marks with oozing of blood at the site of bite. Bite by big four species was estimated to be 30.2% by Saw-scaled viper, 20.8% by Russell's viper, 26.3% by Krait and 22.7%by Cobra.(13)

Suchithra N **et al. (2008)**(14)carried out a prospective study of snake bite cases admitted to Kottayam Medical College, Kerala for a period of one and half year from May 2005 to December 2006. Of the 586 cases, 34% cases had envenomation; 58% of victims were males and 52% belonged to 31-50 yrs age group. 93% of bites occurred outdoor and in 34.5% of venomous bites the snakes were identified. 93.5% had local signs of envenomation. Morality of 3% was recorded. Capillary leak syndrome, respiratory paralysis and intracerebral bleeding were risk factors for mortality.(14)

Alirol E et al. (2010)(6)observed that 90% and 98% of snake bite victims were given tourniquet application as first aid in Nepal and Bangladesh respectively.

28% and20% of victims were given incision in and around bite site as first aid in Bangladesh and North East India respectively.

Inamdar et al in 2010 conducted an 10 year retrospective study in Maharashtra which showed a case fatality rate of 5.4% with higher incidence of mortality among women and neurotoxic bite.(15)

Mohapatra B et al (2011)(16) analyzed the million death survey conducted in India which was nationally representative study with 1,23,000 deaths from 6,671 randomly selected areas in 2001-03.Snake bite was found to be more common among rural population with male predominance. Maximum victims belonged to 15-29 years age group and the bite was more common during monsoon season.0.47% of mortality was assigned to snake bite.(16)

Ahmed SM et al (2012) (17) conducted a prospective study on 113 patients and reported male preponderance of 69.4%, mean lag time (time elapsed between bite and first dose of anti-snake venom) of 5.3 ± 1.4 hours and the mean anti-snake venom dose of 12.3 ± 2.4 vials. They also showed a positive correlation between lag time and total dose of anti-snake venom. The overall mortality was 5.1%.(17)

Data from Tamil Nadu:

Though Tamilnadu has been documented to be among the 13 states with high burden of snake bite with a proportional mortality of 5.3 per 1000 population by Mohapatra et al in analysis of the million death study in 2011, there is a severe paucity of reporting of snake bites from Tamil Nadu.(16)

Vaiyapuri S et al (18) in 2013 conducted a survey among the rural population of Tamilnadu and suggested that the snakebite incidence is higher than previously

reported at 3.9% of those surveyed. Mortality corresponded to 0.45% of the population. They also showed that snake bite caused profound socioeconomic impact on the survivors in terms of cost of treatment. The consequences are severe on long term effects on health, including affecting the ability to do regular work.(18)

These figures stated above clearly point out the fact that the incidences of snake bite that are estimated by the various hospital based studies are just the tip of problem. The actual incidence, mortality and morbidity may be much more than the estimated values stated above.

DISTRIBUTION OF VENOMOUS SNAKES IN INDIA

More than 2800 species of snakes are recognized in the world over, but only 375 of these have front fangs that make them capable of injecting venom during bite. The venomous snakes belong to 5 families. The snakes belonging to the Colubridae family snakes dominates all others types of snakes in numbers, size and distribution.

Earlier studies and books reported that India had about 242 species of different snakes distributed all over the country of which 57 species are of the poisonous type.(19) Currently according to the recent publications India has a total of around 276 snake species in the country. 62 species are poisonous, 42 are mildly-poisonous and 172 are non-poisonous. Among the 62 poisonous species, 20 belong to the sea snake variety and 42 are land dwellers. 38 out of the 42 types of land snakes are distributed in a very small limited geographical areas.(20)The remaining four species are known for the vast majority of snake bites across the country and the ensuing complications and death. Commonly called as the '**big four'** they are the - **Indian Cobra (*Naja naja*), Common Krait(*Bungarus coerulus*), Russell's viper(*Vipera***

***russeli*) and Saw Scaled Viper(*Echis carinatus*)**. They predominantly belong to the families of Elapidae, Colubridae, and Viperidae. Local effects and bleeding are the usual manifestations of the bites of Viperidae, Colubridae and Crotalidae. Neurological symptoms, particularly paralysis are the predominant manifestation of Elapidae group of species whereas paralysis and myolyis are the predominant mode of injury by Hydrophidae.(21)

One of the widely accepted concepts in Indian snake venom discussions and research is the notion of the so called ‘‘Big 4 Snakes of Medical Importance,’’ which includes the Russell’s viper (*Daboia russelii*), the saw scaled viper (*Echis carinatus*), the Indian or spectacled cobra (*Naja naja*), and the common krait (*Bungarus caeruleus*). These 4 snakes have been believed to cause the vast majority, if not all, fatalities due to snakebite. Among these four snake species, no particular species is more dangerous, and any of the four bites is considered dangerous than the other. Few reasons for them being called the ‘big four’ include:

- **Indian Cobra**- One of the most wide spread in distribution. As it occurs in areas with high density of human settlements, particularly attracted by rats it has higher chance of human interaction and confrontation than the other species.
- **Common Krait**- Is included because of its potent venom and many a times the patient does not realise he has been bitten. Fang marks are difficult to find and sudden onset neurological paralysis is common.
- **Russell’s viper** – Causes severe coagulation abnormality associated with severe local reactions and bleeding and can lead to compartment syndrome. Endemic areas are characterised by high frequency of bites.

- **Saw Scaled Viper**–Has a specific venom component called Ecarin which can lead to life threatening envenomation causing death secondary to bleeding.(20)

Some species of Indian snakes such as the King cobra (*Ophiophagus hannah*) are recognised to be capable of causing severe and lethal envenoming. But comparatively the fatalities attributed to this and other dangerously toxic species of snakes are relatively negligible owing to the fact not only that these species of snakes are rare in distribution as well as there is very minimal number of bites and contact with human population due to these rare dangerous species of snakes.

WHO in 1981 developed and published a methodology to identify the snakes that are of medical significance. The proposed WHO classification was: (22)

- **Class I**— Snake species which commonly cause serious disability or death.
- **Class II**— Snake species which are uncommon causes of bites but are capable of causing serious effects once envenomation has occurred.
- **Class III**— Snake species which are known to commonly cause bites but incidence of serious effects due to envenomation is very uncommon.

This methodology may be considerably more valuable than the **‘‘big 4 ’’** concept, particularly in view of the fact that reliable epidemiological data regarding snake bite and envenomation are not readily available in India. The contribution made by each particular species of snake to the overall morbidity and mortality figures isunknown.In view of the above facts, a validated methodology such as the definition given by the World Health Organization, which can provide the ability to assess

medical significance of the snake bite without particular reliance on specific numbers alone, is a much more useful tool for medical professionals and doctors practising in the community.

The Snakes of Medical importance in India that are listed by the World Health Organization are as follows:(22,23)

- **Class I**
    - Cobra
    - Russell's Viper
    - Saw-Scaled Viper
- **Class II**
    - Krait
    - King Cobra
    - Hump nosed pit viper
    - Mountain pit viper.
- **Class III**
    - White Lipped Pit Viper and other non-venomous species

There are about 104 species of snakes in South India of which only 37 are poisonous. The poisonous snakes commonly seen in Tamilnadu are Russell's Viper (Vipera russelli or Vipera duboi), saw scaled or carpet viper (Echis carinatus), cobra (Naja naja), Indian krait (Bungarus caeruleus) and sea snakes.

Very often the hunting habitat of these four snakes may overlap. But each one has its own special microhabitat and food preferences which lead to few regions having a higher incidence of a particular snake type. One example is a recent study

conducted in South India which reported a significant number of cases of snake envenomation among plantation workers in Kerala due to bites by the Malabar pit viper and Hump nosed pit viper. These two snake species are emerging as medically important species and unfortunately ASV (anti-snake venom, antivenom, antivenin) for these species is not available in India.(6)Hence, it's essential to study the other venomous species which are medically important rather than focusing on the big four species.

Figure 1: The Russell's viper (Vipera russelli or Vipera duboi)

Figure 2: Saw Scaled Viper or Carpet Viper (Echis Carinatus)

Figure 3: The Indian or spectacled cobra (*Naja naja*)

Figure 4: The common krait (*Bungarus caeruleus*)

PHARMACOLOGY OF SNAKE VENOM

Snake venom is toxic saliva secreted by modified parotid glands which are located in the snake's mouth, below and behind the eye. The purpose of venom is two folds. Firstly to immobilize or kill the prey before it is swallowed and secondly, to aid digestion by breaking down the prey's tissues. Often, when the snake bites it prey, the enzymes present in its venom start breaking down the prey's tissues even before the prey is dead or swallowed.(8) For snakes, venom is not a weapon of mass destruction nor is targeted at human race.

Venom is a clear, amber colored fluid when fresh. It is most complex of all poisons and contains more than 20 different components. The venom mainly consists of proteins which include variety of enzymes, non-enzymatic polypeptide toxins and non-toxic proteins. Other than proteins, the venom also consists of carbohydrates, metals, lipids, free amino acids, nucleotides and biogenic amines. Of the components, the more lethal and deleterious fractions are peptides and proteins of low molecular weight (6000 to 30,000). The polypeptide toxins (non-enzymatic proteins) are categorized into neurotoxins and hemorrhagens.

Neurotoxins:

The neurotoxins are most abundantly found in elapid (Cobra, Krait) and hydrophid (sea snakes) venom. They are also present in lesser quantities in some vipers such as Russell's viper of South India and Srilanka. Neurotoxins act either at pre-synaptic or post-synaptic levels. The Krait venom acts pre-synaptically on the nerve terminals. It causes initial release of acetylcholine but then damages the nerve terminal and prevents further release. It is for this reason that Krait envenomation victims do not respond to Anticholinesterase therapy and often take longer time to recover than Cobra envenomation victims.(10,12) Cobra venom acts post-synaptically by competing with acetylcholine for receptors at neuromuscular junction and leads to curare like paralysis. The earliest sign of neurotoxic paralysis is ptosis followed by external ophthalmoplegia. Paralysis involves the proximal muscles first and then the distal muscles and recovery occurs in the reverse order. The internal ophthalmoplegia is attributed to autonomic dysfunction.

Hemotoxins:

Hemorrhagins (Zinc metalloproteinases) damage the endothelial lining of blood vessel walls causing spontaneous systemic haemorrhage. The enzymatic components of venom consists of enzymes such as Phospholipases, Hyaluronidase, Hydrolases, Procoagulant enzymes, Acetylcholinesterase. The pathophysiological manifestations of these enzymes are clearly evident in case of viper venom. Procoagulant enzymes present in Russell's viper which stimulate the blood clotting cascade are:

a. RVV-X—A glycoprotein activates factor X by calcium dependent reaction, factor IX and protein C

b) RVV-V— An arginine ester hydrolase activates factor V.

Saw scaled viper venom contains a Zinc metalloprotein i.e. ecarin which activates prothrombin. The procoagulant enzymes activate clotting cascade and result in formation of fibrin in the blood stream. Most of this is immediately broken down by the body's own fibrinolytic system. Eventually, within 30 minutes of the bite, the levels of clottingfactors become so depleted (consumption coagulopathy) that the blood will no more clot. Deciding the potency of the venom is problematic. It is obviously not possible to determine this by experiments on humans. Experiments conducted on mice by Ernest and Zug indicate venom of Hook nosed sea snake and Russell's viper are more potent. But when we consider the land snakes, these do not confirm to the general experience in this two snakes. Whitaker and Captain while dealing with Common Krait, describe it as producing "the most potent venom of all our land snakes". Going by findings elsewhere also, this observation has to be expected as correct. One of the curious feature of venom is that its composition not only differs from species to species, but differs even among individuals of the same

species inhabiting different geographical areas and even among the individuals of same litter. Thus, ASV needs to be prepared from species prevalent in the particular region.(6,20,24)Potency of the venom differs depending on various factors such as age and health of the individual snake. New-born and very young snakes have more potent venom than adults. This is Nature's way of compensating for lesser quantity in the new born and the very young. There may be seasonal variation in the quantum and potency of the venom. Venom produced soon after hibernation is very potent whereas that produced during moulting phase is less toxic. Male snakes produce more venom than female snakes.(25)

CLINICAL FEATURES OF SNAKE ENVENOMATION(26–28)

The symptom with which the patient presents depends upon the composition of the venom. Depending upon the species, the following symptoms may be seen.

Local symptoms

- Puncture marks of the fangs.
- Pain
- Oozing from the bite wound.
- Swelling
- Discoloration
- Necrosis.

Systemic symptoms

The symptoms may vary in different individuals and with different species of snake but it can be classified into neurotoxic, haemotoxic and myotoxic based on predominant symptoms.

- **General -** nausea, vomiting, malaise, abdominal pain, weakness, drowsiness, prostration.
- **Cardiovascular system** - dizziness, faintness, shock, hypotension, cardiac arrythmias, pulmonary oedema.
- **Hemostatic disturbances -** Bleeding from bite site, I.V.lines and old partly healed wounds. Spontaneous bleeding from gums, epistaxis, bleeding into tears, hemoptysis, hematemesis, rectal bleeding or melaena, hematuria, bleeding per vaginum, bleeding into skin, mucosa, intracranial hemorrhage (meningism from subarachnoid hemorrhage, lateralizing signs and/ or coma from intracerebral bleed). These symptoms are seen in viper envenomation.
- **Neurological symptoms** such as drowsiness, paraesthesiae, taste and smell abnormalities, ptosis, ophthalmoplegia (external and internal), facial muscle paralysis, aphonia, difficulty in deglutition, respiratory and generalized flaccid paralysis are seen in elapid snakes and also in Russell's viper bite found in South India and Srilanka.
- **Myotoxic** symptoms such as skeletal muscle breakdown (rabdomyolysis) are seen in Sea snakes. It is characterized by generalized pain, stiffness and tenderness ofmuscles, trismus, myoglobinuria, hyperkalemia, cardiac arrest, acute renal failure.

- **Renal system** is often involved in Russell's viper bites, Sea snake bites andcauses loin pain, hematuria, hemoglobinuria, myoglobinuria, oliguria/anuria, uraemia (acidotic breathing, hiccups, nausea, pleuritic chest pain). Saw scaled viper is not known to cause renal failure unlike Russell's viper.
- **Gastro intestinal system** - Acute abdomen in Krait bite is due to neuromyositis(13)and in Viper bite due to gastro intestinal and/or retro peritoneal bleeding.
- **Ophthalmic** – Ptosis is the earliest sign indicative of neurotoxiciy followed by ocular muscle palsy. Hemorrhages into conjunctiva, anterior chamber, vitreous orretina, lid edema, conjunctival chemosis, retinal and optic nerve oedema, optic neuritis, optic atrophy and rarely cortical blindness can be seen.(29–31)
- **Endocrine (Acute pituitary/ adrenal insufficiency) system –** It is often reported with Russell's viper envenomation. It has two phases -*Acute phase* is characterized by shock, hypoglycaemia and *Chronic phase* (months to years after bite) manifests with weakness, loss of secondary sexual characters, amenorrhoea (Sheehan's syndrome), testicular atrophy, hypothyroidism.(32,33) Sometimes, patients with neurotoxic envenomation may present with brainstem death like signs such as areflexia, dilated & non reacting pupils and no spontaneous respiratory efforts. Confirmatory tests for brainstem death like Electro cerebral silence on EEG for at least 30 minutes and absence of blood flow in 4 vessels cerebral angiography should be done. Prolonged ventilator support may revive the patient (in case the patient is not brain dead).(34–38)

- Other complications which can occur in snake bite patients are - Acute pulmonary oedema(39), extensive necrosis requiring amputation of the limb, chronic ulceration, osteomyelitis with malignant transformation and neurological sequelae.

MANAGEMENT OF SNAKE BITE

World Health Organisation (WHO/SEARO) has published guidelines that are specific for the South East Asia region countries such as India for the clinical management of snake envenomation's. These guidelines were published in the supplementary issue of the South East Asian Journal of Tropical Medicine and Public Health.(26,28)WHO/SEARO guidelines are currently universally followed. The following management is as per the WHO guidelines:

First aid (20,26,40)

First aid is the procedure to be carried out immediately or very soon after the bite before the patient is taken to a hospital or dispensary. The most important thing in first aid is **'Do No Harm'** to the victim than anything else. WHO established a Snakebite Treatment Group in 2004 to tackle the problem of snake bite in the world. The primary objective of the group was to identify problem areas in terms of snake bite so that the current high level of snake bite mortality that could be reduced.In July 2006 India convened a National Snake Bite Conference and developed national protocols for first aid after snake bite and treatment following envenomation.

The first aid that was recommended by the committee is based on the pneumonic:

"Do it R.I.G.H.T".

R = Reassurance of the patient. This is very essential as a majority if the bites are from non-venomous species and less than half of the bites from venomous species

actually envenomate. Just fear is capable of psychological shock causing death so reassurance is important.

I = Immobilization of the limb affected similar to stabilisation of a fractured limb. Children can be carried to the hospital. It is very essential to immobilize the patient also**(masterly immobility).** Do not apply any pressure in form of tight compressions or tourniquets that blocks the blood supply. If a vehicle is not available for transportation, victim can be carried on a stretcher, basket or a light bedstead (charpoy) to comply with masterly immobility. Immobilization reduces the venom absorption and circulation.

G.H = **G**et to **Hospital** Immediately or as early as possible. Traditional remedies have been shown to have no benefit in treating snakebite.

T =Tell the doctor, about the incident and signs and symptoms the victim manifests with.

Unfortunately, most of the popular, traditional, affordable and locally available first aid methods such as tourniquets, incision and drainage, wound washing, stone application, electrical therapy, cryotherapy, pressure immobilization method, squeezing of the wound and sucking/suctioning are proved to be useless or even dangerous and precious time is lost in applying them and cause further delay in approaching to the health care centres. The only benefit of these methods are, they can give reassurance to the anxious victim and reduce the psychosomatic effects and may act as placebo in non-venomous snakebites. **But these methods are not medically helpful and are not to be practiced.**

Caution: Never attempt at killing the snake as it is mere waste of time and leads to other victims. If killed, carry it very carefully to the hospital for identification by the doctor. Care should be taken while handling even the dead snake as even the severed head can bite and this reflex is present up to one hour after death of the snake. Every case of snake bite should be taken to doctor. The victim must be admitted and observed for at least 24hours for signs and symptoms and treated accordingly. Even in known cases of non-venomous snake bite, victim should be taken to doctor for administration of Tetanus toxoid.

Precautions against snakebite(20)

'Prevention is always better than cure'

Snake bites can be prevented by simply learning the type of snake inhabiting in respective regions and learning their behaviour and habitat.

a. Carry a torch while walking in the dark and 'mind the step'.
b. Clothing covering the legs such as full pants and protective foot ware such as shoes or gum boots act as barrier and minimize the venom injected**.**
c. In snake infested areas, make sure that snakes don't refuge in shoes, pockets of coats, trousers before they are worn.
d. Tea, coffee plantation workers should be vigilant while working as bushes are favourite habitat of Pit vipers.
e. In areas where Common Krait occurs, sleeping on the floor should be avoided.
f. Never provoke a snake. Generally, snakes avoid confrontation with human beings. Learn to recognize the warning sign given by the snake before it strikes such as stopping of flickering of tongue, hissing (Russell's viper), hood raising (Cobra),

coiling of body into ‘S’ shape (Saw-scaled viper), vibration of tail (Bamboo pit viper). Further provocation of snake on displaying warning sign leads to bite and envenomation.

g. If the snake is likely to strike, keep yourself at a safe distance. When a snake is poised to strike, it strikes with tremendous speed.
h. Moulting snakes have foul temper and are very aggressive.
i. Younger snakes are more easily irritable and quicker to strike than an adult. New born of venomous species have fully operational fangs and enough venom to cause severe envenomation in humans.
j. Do not indulge in bravado while handling or dealing with venomous snakes. Even a momentary carelessness even by an experienced and careful person can prove to be a terrible mistake.
k. If a snake has bitten any person, neither he nor anyone else should remain at the site as the snake keeps lurking around in the vicinity due to its peculiar mode of hunting its prey at leisure
l. Do not venture out alone into terrains where snakes are likely to be found. Go atleast in pairs. Both the companions should be well informed about snakes as they can take care of each other during emergency.

Anti-snake venom (ASV, antivenin, anti-venom) (25)

Anti-snake venom is an immunoglobulin that is purified from the serum of a horse or sheep which have been immunized with the venom of one or more snake species. Enzyme refined F(ab)2 fragment of IgG type is what is usually used. In 1887, Henry Sewell laid the foundations of antivenin therapy by his experiments conducted

in the University of Michigan, USA, on various snake venoms. Albert Calmette, a student of Louis Pasteur (founder-Director of Pasteur Institute in Saigon, Vietnam) followed up the research done in US and discovered ASV in 1891. The first antivenin became commercially available in 1927 in USA.

ASV in India

ASV can be of **monovalent** (specific to venom of single species) or **polyvalent** type (specific to venom more than one species). **In India, only polyvalent ASV is available. It's effective against only the 'Big four' species**. ASV is ineffective against other species like Hump nosed pit viper and others. One ml of polyvalent ASV can neutralize 0.6 mg of Cobra and Russell's viper venom and 0.45 mg of Krait and Saw-scaled viper venom. One vial of ASV (10 ml) can neutralize 6mg of Russell's viper and Cobra venom. In India, ASV is manufactured in public sector by Haffkine Biopharmaceuticals Ltd, Mumbai; Bharat Serums and Vaccines Ltd, Mumbai; King Institute, Chennai. M/s.Vins Bio-products Ltd, Hyderabad; Serum Institute, Pune and Biological 'E' Ltd, Hyderabad in private sector also produce ASV. In an Indian study, it has been found that the Specific venom neutralizing property of ASV depends upon the geographical origin of the snakes used for procuring venom for immunization. It was observed that the dose of ASV required to treat victims at Pondicherry was double the dose required for victims at Maharashtra. The ASV used for treatment was obtained from Pune and Mumbai respectively where the Saw scaled viper venom is procured from the snakes caught in Western Maharashtra. **The effectiveness of ASV produced in India is also questionable against venom of Sochurek's Saw scaled viper found in Rajasthan. Thus, it is advised to prepare ASV from venom procured from snakes from same geographical areas.** ASV is

scarce and costly. The lyophilized venom supplied to institutions for manufacturing ASV is costly. The Irula Snake Catchers' Industrial Cooperative Society, Vadnemeli, Tamil Nadu, is a major supplier of lyophilized snake venom and chargesRs.10,000 per gram of cobra and Russell's viper venom and Rs. 30,000 to 80,000 per gram of Saw scaled viper and Common Krait venom. Hence, ASV is very valuable and should be used judiciously.

Administration of ASV (26)

Administration of ASV to any patient with history of snake bite without any signs and symptoms of envenomation should be strongly discouraged as the patient is unnecessarily exposed to ASV which has risk of life threatening reactions an sensitization apart from ASV being scarce.

Indications(26,28)

ASV should be administered only if and when the patient has proven signs of either systemic or local envenomation. **Only unbound venom present in the blood stream or tissue fluid is neutralized by ASV.**

Systemic envenomation

a) Evidence of Hemostatic abnormalities: spontaneous systemic bleeding (clinical), coagulopathy (20 minute WBCT or other laboratory) or thrombocytopenia.
b) Evidence of Neurotoxic envenomation: ptosis, external ophthalmoplegia, muscle paralysis, inability to lift the head etc.
c) Evidence of Cardiovascular abnormalities: hypotension, shock, cardiac arrhythmia, abnormal ECG.
d) Acute renal failure: oliguria/anuria, increased blood Creatinine/ Urea.

e) Persistent and severe vomiting or abdominal pain.

Local envenomation

a. Local swelling involving more than half of the bitten limb (in the absence of a tourniquet) or severe swelling of the digits (toes and finger).
b. Rapid extension of the swelling within few hours of bite (beyond ankle or wrist when bite on hands or feet).
c. Development of an enlarged tender lymph node draining the bitten limb.

Anti-Venom Reactions:

There are predominantly three types of reactions:

1. Early(anaphylactic) reactions
2. Pyrogenic reactions
3. Late (serum sickness-type) reactions.

The incidence of early and late reactions can be decreased by pre-treatment with antihistamines, corticosteroids and subcutaneous adrenaline. **Early antivenin reactions** cannot be predicted by the usual hypersensitivity tests as they are not the typical IgE-mediated reactions to equine serum proteins. Complement is activated by the antivenins in vitro. The complement activation along with immune complex formation in vivo leads to the clinically similar reactions that this hypersensitivity is associated with. Aggregates of Ig G probably activate the complement system. The hypersensitivity reactions may start as early as 10 min. They can be delayed till within 10 minutes to as late as 180 minutes. The prominent features are itching, fever, cough,

nausea, tachycardia, palpitations. The reported incidence of antivenin hypersensitivity can vary from 3% to 54%.(41)

Literature from the WHO states that ASV hypersensitivity reactions increase with the dose of ASV used. They also state that these reactions decrease with the use of refined ASV is used. But this may not hold good due to various reports by recent studies.(41)Patients must be observed carefully for at least three hours post ASV administration in order not to miss the mild reactions and thereby prevent wrong attribution of deaths to envenoming itself. Though 40% of the patients having early reactions may show features of severe reactions such as systemic anaphylaxis with bronchospasm, angioedema and rarely hypotension, deaths are usually rare in this group. Early reactions can be readily treated by subcutaneous adrenaline given at a dose of 0.5 to 1ml of 0.1 % solution (1:1000, 1 mg/ml)in adults. Antihistamines (e.g.chlorpheniramine maleate and others) should be given by intravenous route to neutralize the effects of anaphylaxis caused by histamine release.

Pyrogenic reactions occur as a result of contamination of the ASV and the diluting fluid by endotoxin like substances. They are characterised by high grade fever developing 1-2 hours post treatment. The presenting features are usually rigors, warm extremities suggesting vasodilatation and a later hypotension caused by fall in blood pressure. Febrile seizures may occur in predisposed children. Emergent cooling measures must be undertaken immediately.

Late (serum sickness-type) reactions develop 1 to 12 days (mean 7 days) after treatment with antivenin therapy. These reactions may be dose related and the incidence and speed of develop of these reactions is higher with higher the dose of ASV administered. The main clinical features include low grade fever, itching, arthralgia, mainly of the temporo-mandibular joint, lymph node enlargement,

periarticular swellings with effusions, mononeuritis multiplex, mild albuminuria and rarely encephalopathy. These reactions respond to antihistamines such as chlorpheniramine in mild cases. More severe cases of late reactions may require corticosteroids usually given over a course of five days.

COMPLICATIONS OF SNAKE BITE

1) Hypotension

Very scanty information exists in literature regarding this aspect of snake envenomation. The incidence of hypotension in various studies ranges from 10- 26 percent with a study from Medical College in Kottayam, Kerala showing the incidence as 22 % where as a study from Jammu medical college showing an incidence of 10%. A series of 46 cases of fatal snake envenomation from Thailand showed that 26% of the mortality was due to uncorrected hypotension. Worldwide the snake species causing hypotension commonly are the Burmese Russell's viper, Vipera palestini and the North American rattle snake.

Snake causing hypotension in pregnancy can be caused by exaggerated supine hypotension syndrome or by antepartum haemorrhage causing intrauterine death.(42,43) Hypovolemia becomes an important contributing factor for both early and late onset hypotension. The causes include excessive sweating due to kinin system activation or the venom itself, vomiting and diarrhea. Fluid restriction practiced by the local traditional healers also contributes to hypovolemia. Other important cause is the generalized increase in capillary permeability seen post envenomation. This causes a sort of **capillary leak syndrome** that is observed

especially secondary to viperine bites and patients additionally develop both conjunctival and facial oedema. Loss of plasma secondary to a severe local reaction at the injured area could be another cause of hypovolemia.(44,45) Internal and external bleeding can cause hypovolemia which can be due to various factors such as coagulation failure caused by Disseminated intravascular coagulation, platelet function and number abnormalities, and also the venom toxins such as haemorrhagins which produce endothelial damage causing seepage of red cells across the capillary walls. Venom also causes release of histamine and serotonin which only further aggravate the vasodilation leading to more hypotension. SIRS and DIC by themselves can produce hypotension and shock by vasodilation. Other rare causes include myocardial dysfunction causing low ejection fraction, acute pituitary failure or adrenal haemorrhage. Antivenin therapy can also cause early onset hypotension as a complication

2) Respiratory failure:(46–48)

Severe cases of Elapid poisoning mainly affect the muscles of eyes, throat, tongue and chest wall causing opthalmoplegia and paradoxical respiration ultimately leading to respiratory failure. These toxins act both pre-synaptic as well as postsynaptically. The respiratory failure is mainly type II causing both hypoxia and hypercapnia secondary to CO2 retention. The severity of respiratory failure is related to the dose, potency, site of venom entering the body and timely medical support with Anti snake venom.

3) Renal failure:

The causes of renal failure include hypovolemia that occurs due to various factors described above such as disseminated intravascular haemolysis, direct venom induced toxicity causing papillary necrosis and rarely anti-snake venom induced acute interstitial nephritis. ASV administration early in the course of treatment has been associated with decreased incidence of ARF. ASV does not provide complete protection against this complication. A study done by Merchant et al in 1989 in 29 cases of snake bite with renal failure showed renal histology of tubular necrosis in 35%, cortical necrosis in 24% tubular degeneration in 17% and glomerular changes in 17%.(49) The significant glomerular changes seen were ballooning of glomerular capillaries in 59%, splitting of glomerular basement membrane in 40.7%, swelling of endothelial cells in 29.6% and focal proliferation of mesangial cells in 17%.(49) Development of oliguria within 24 hours of snake bite and cortical necrosis were associated with higher mortality.(49) A significant factor involved in the pathogenesis of viper bite-induced glomerular disease may be mesangiolysis that has been shown experimentally.(50)Haemorrhagic Glomerulonephritis is very rare.(49–51)

4) Gangrene:

Local necrosis which when neglected can result in complication of gangrene. Wound need to be frequently examined for evidence of necrosis and gangrene. Early signs include formation of blisters, blackening or blanching, loss of sensation over the affected area and a characteristic smell of tissue necrosis. As the risk of secondary bacterial infection is very high, spontaneous sloughing of the necrotic tissue should not be allowed. The dead tissue must be removed under spinal or local anaesthesia with aseptic precautions as soon as possible.

THE PROBLEM AND IMPORTANCE OF COAGULOPATHY IN SNAKE BITE

Snake venom is a combination of cytotoxins, hemotoxins, neurotoxins and myotoxins. Earlier, the venom of a particular snake was considered to be one kind only, either hemotoxic or neurotoxic, and this erroneous belief still persists in many parts of the world where updated literature is hard to access.(52)Snake venom is a complex mixture consisting of many active agents. Most of these agents have multiple effects and very few components, if any, may have a single 'pure' effect. "Procoagulant" as well as "anticoagulant" venom components have been identified in *in vitro* test systems. "Procoagulant" snake venom components may cause *in vivo* massive intravascular coagulation leading to circulatory arrest and rapid death. Smaller doses of procoagulant venom components applied to large organisms as in the case of snake-bite accidents in humans, may cause a consumption coagulopathy with localized or generalized bleeding.(53) Further workers like R.M. Kini et al have shown several snake venom constituents especially enzymes such as phospholipase A2, proteinases, nucleotidases or L-amino acid oxidase interfere in platelet aggregation whereas some venom factors induce platelet agglutination.(54)

A case series of snake bites conducted among children in Australia showed that all the children with clinical signs of envenomation demonstrated coagulopathic laboratory features when assessed by prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen levels and fibrinogen degradation products (FDP)s. This observation was made in all cases, independent of the species of snake causing the bite.(55) Hence it indicates that even snake bites which have been classically referred to as classically neurotoxic in earlier days have some amount of coagulation dysfunction associated.

Thereby the study concluded that assessment of derangement in coagulopathy could provide not only a highly sensitive, specific testing but also an reliable indicator of envenomation.(55) In a 5 year retrospective analysis by Chew et al found that even snake bites due to Elapidae family such as Cobra which are classically referred as 'purely' neurotoxic there were several cases of hemotoxicity also occurring concurrently.(56)

Haematological alterations

- **Haemoglobin:** Fall in haemoglobin can be due to various causes such as loss of blood into the affected limb, seepage of red cells secondary to increased capillary permeability and hemolysis secondary to the venom itself.

Disseminated Intravascular Coagulation (DIC)

DIC is a dangerous complication which can be very fatal if unrecognised. Viper bites are especially known to lead to the occurrence of DIC. The underlying pathophysiologic process is characterised by extensive and diffuse intra vascular activation of clotting cascade leading to depletion of coagulation factors. This overutilization of clotting factors and platelet causes an acquired haemostatic defect in the clotting process. The whole process gets triggered by the snake venom which leads to simultaneous activation of several steps in the coagulation process. Hageman factor (Factor XII) is directly activated by the venom components. The toxins also induce accelerated tissue factor expression on the endothelial cell surface. Cell surface activation with the tissue factor then further accelerates the other reactions. Micro

thrombi and emboli are deposited throughout the micro vascular network as a result of this extremely potent thrombogenic stimulus. The early thrombogenic phase is later followed by a phase involving consumption of procoagulant factors and secondary fibrinolysis. Continued formation of fibrin followed by fibrinolysis leads to haemorrhage caused by depletion of coagulation factors, platelets and anti-haemostatic effect of fibrin degradation products. DIC may be acute or sub-acute usually. Rarely it may be chronic. Snake bite is one of the important causes of consumptive coagulopathy.(57)The severity of clinical presentation depends on the stage of the DIC. Severe cases can have extensive bleeding from the mucous membranes and sites of breach in skin continuity. Venepuncture and catheter insertion sites may present with continuous ooze. Rarely features include development of acrocyanosis and pre-gangrenous changes in the digits due to thrombosis. Similar changes can be seen in the genital area and nose. These areas are characterised by markedly reduced blood flow secondary to thrombosis and vasospasm. Patient can have MODS (multi organ dysfunction syndrome) due to extensive ischemia caused by micro vascular thrombosis. Thrombotic process affecting the large vessels can cause venous as well as arterial thrombosis leading to various manifestations such as deep venous thrombosis which can reversible as well as ischaemic stroke.(58–60) Thrombocytopenia can occur with rattlesnake poisoning.(61)

Early recognition of DIC followed by prompt institution of appropriate therapy coupled with intense laboratory monitoring help in reducing mortality due to DIC. Low platelet count along with fragmented RBS's called as schistocytes constitute the predominant laboratory manifestations. These are formed due to trapping and damage of red cells in the fibrin thrombi. Prothrombin time, Activated Partial Thromboplastin time and Thrombin time are prolonged. Secondary fibrinolysis

leads to low fibrinogen levels and elevated levels of fibrin degradation products (FDPs). Such very low fibrinogen levels can be associated with internal bleeding like intracranial or intra-abdominal bleeds.(62)

Venom induced consumption coagulopathy

Concept of venom induced consumption coagulopathy (VICC) being different from disseminated intravascular coagulation (DIC)(63)

Isbister et al have been the proponents of the concept of venom induced consumption coagulopathy (VICC).(63) They say that VICC has many times been likened to DIC because of the elevated D-dimer, prolonged PT and low fibrinogen but it does not have other important features that are associated with DIC, such as systemic micro thrombi. Also VICC time course differs by rapid onset and resolution. The mechanism of initiation of coagulation activation may be different. The problem of the overlapping clinical syndromes of thrombotic microangiopathy and VICC in snake envenoming could be the most likely reason for researchers developing the mistaken idea that snake envenomation causes DIC.(63)

LABORATORY INVESTIGATIONS

Routine investigations

- Leucocytosis is commonly present with neutrophil predominance.
- Anaemia follows the initial haemoconcentration resulting from extravasations of plasma.

- Thrombocytopenia is common after bite by Russell's viper and can be venom induced or secondary to DIC. Bites by Saw scaled viper also cause low platelet levels universally.
- Prolonged whole blood clotting time usually indicates low fibrinogen levels. Other sensitive methods to diagnose defibrination are assay for FDP's and fibrinogen level testing.
- Rapid rise in creatinine phospho kinase, associated with hyperkalemia and elevated myoglobin is diagnostic of rhabdomyolysis.
- Black or brown coloured urine on urinalysis is suggestive of intra vascular haemolysis causing myoglobinuria.
- Electrocardiographic abnormalities include bradycardia, ST-T changes, first or second degree heart blocks. Tall T waves can be seen due to hyperkalaemia.
- Pituitary and renal failure are known to occur. This may cause changes in the hormonal profile of the patient.

CLOTTINGTIME:

Clotting time will be prolonged in most cases of moderate to severe envenomation. 20 minute whole blood clotting time is a simple and sensitive bedside test of systemic envenomation.

CLOT OBSERVATION TEST:

This is a very simple test that assesses the status of blood coagulation. 3-5 ml of freshly drawn venous blood is kept in a clean glass tube 20 minutes and left undisturbed. After 20 minutes the tube is tipped to see whether the blood has clotted.

If the blood remains unclotted even after 20 minutes, then it is a sure sign of envenomation.(64,65)

CLOT RETRACTION TEST:

This test is done similar to the above test but is observed for a longer period. 5 ml of venous blood is taken in a completely dry test tube which is kept slanting. Periodical examination of the tube is conducted. Not only must the venous blood sample clot in less than 20 minutes but also the clot must retract in 2-6 hours. Straw coloured serum must be separately seen. Envenomed patients have defective or prolonged abnormal clot retraction times.(66)

PROTHROMBIN TIME:

Fibrin production by means of the extrinsic and common pathways requires factor VII, tissue thromboplastin, factor X, factor V, prothrombin and fibrinogen. Both the pathways are measured by prothrombin time. The assay involves plasma re - calcification in the presence of excess tissue factor. Unlike activated partial thromboplastin time this test does not require contact activation. It bypasses the intrinsic pathway and the factors involved. Platelet numbers do not affect the test because tissue thromboplastins in the sample contain phospholipids that act as platelet substitutes. Of the five coagulation factors measured by the plasma PT (fibrinogen, prothrombin, factors V, VII, X), three factors namely prothrombin, factor VII and X are vitamin k-dependent and can be affected by coumarin like drugs. As a result, the plasma PT is most widely used for controlling dose of oral anticoagulant therapy. The plasma PT usually is prolonged when the plasma levels of any of the requisite factors are lower than 10% of normal. It is more sensitive to deficiencies of factors VII and X

than deficiency of fibrinogen and prothrombin. Multiple modified techniques and various thromboplastins have been developed to increase the utility of the PT in the control of coumarin based anti-coagulant therapy.

The expression of the PT as a percentage of normal is not recommended. This is because the dilution curves used to arrive at this figure may be misleading and often have little quantitative meaning. Use of the standardised International normalized Ratio (INR) in monitoring oral anticoagulation therapy is recommended. The plasma PT performed with bovine thromboplastin or with Thrombotest reagent is abnormal in individuals affected with certain genetic variants of factor IX deficiency.

The Russell's viper venom initiates coagulation by the direct activation of factor X and does not require factor VII due to the presence of an enzyme. Therefore "One Stage Prothrombin Time" performed with this venom (called the Stypven time) can reliably distinguish between deficiency of factor X and factor VII.

ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)

The Activated Partial Thromboplastin Time is a simplest test of the intrinsic pathway and common pathways of coagulation cascade. The test involves recalcification of a mixture of plasma and phospholipid platelet substitute, leading to formation of fibrin at a normal rate. This can happen only if the clotting factors involved in the intrinsic pathway namely prekallikren, HMW kininogen, and factors VIII,IX, X, XII and factors in the common pathway i.e. factors V, X, prothrombin and fibrinogen are present in normal amounts. Various kinds of platelet substitutes may be used, such as brain chloroform extract, crude cephalin fractions as well as soybean phosphatides (inosithin). In the APTT test, in order to make the test

unaffected by the number of platelets remaining in the plasma such platelet substitutes are provided in excess. These platelet substitutes which are only partial thromboplastins, are incapable of activating the extrinsic pathway by themselves, which requires additional complete tissue thromboplastin. Thus, the Partial Thromboplastin Time can bypass the extrinsic pathway and is unaffected by factor VII. Other uses of the assay include detection of factor deficiency, screening for the lupus anticoagulant, and to monitor anticoagulation for patients on heparin.

The Partial Thromboplastin time is more sensitive to deficiencies of factor IX and VIII than to deficiencies of factor XII and XI or factors involved in the common cascade. But with most of the techniques used, the test is abnormal if plasma level of any of the essential factors is less than 15 – 30 % of the normal. The assay thus can indicate some mild coagulation factor deficiency disorders. However, this ability of the assay to detect mild coagulation factor deficiency is reagent dependent. Certain reagents may not detect factor deficiency even as low as 5 – 10%. Like all other one stage tests, the PTT value may be shortened by high levels of a single factor, most common factor being factor VIII. Thus in summary, a short PTT could signify any of the various hypercoagulable states, but very high levels of any of the factors involved in the intrinsic pathway or the common pathway may mask deficiencies of other factors.

Originally, contact activation used to be provided by the glass tube. Lately the addition of other activators, such as Ellagic acid or particulate silicates (Celite or kaolin) is shown to provide more optimal and standardized contact activation, and thus represents a significant improvement over the original test which was non activated. Currently the activated PTT (APTT) is routinely used assay to evaluate intrinsic coagulation pathway. The APTT of prekallikren (Fletcher factor) deficient

plasma is abnormal when it is done by standard methods using particulate activators (Celite or kaolin). This abnormality can be minimized or abolished by methods like protracted contact activation for 15 minutes, as compared with 2-3 minutes used in the standard technique. The APTT may be normal in prekallikrein deficiency patients when ellagic acid (soluble activator) is used.

THROMBOELASTOGRAPHY (TEG/ROTEM):

Thromboelastography was originally described in 1948 by Dr Hellmut Hartet at the University of Heidelberg.(67) Thromboelastography monitors coagulation cascade as a whole dynamic process unlike traditional tests which reveal isolated information at various points in the process of clotting.(68)TEG is a dynamic study of process of coagulation, which mechanically studies the process of fibrin formation as well as platelet aggregation followed by fibrinolysis.(68)

Difference between TEG and ROTEM: They are in fact two analogous systems that are commercially available;

- ROTEM -TemInternational GmbH, Munich, Germany
- TEG- Hemoscope Corporation, Niles,IL.

Both use the same technique described by Hartert with slightly different nomenclature and technical differences. The primary hardware difference between the systems is that TEG operates by moving a cup in a limited are (±4°45^{0}every 5s) filled with sample that engages a pin/wire transduction system as clot formation occurs whereas the ROTEM has an immobile cup where in the pin/wire transduction system slowly oscillates(±4°45^{0}every 6s).(69)

Measurement technology:

The TEG measures the viscoelastic properties of blood in vitro. Blood sample (typically 0.36 ml) is placed into a cuvette (cup) which is rotated gently through 4º 45´ (cycle time 6/min) to imitate sluggish venous flow and activation of coagulation. Various patterns of changes that occur in the forces of shear-elasticity based on the type of blood sample taken can be documented on a graph. These patterns help us to determine of the kinetics of clot formation, clot growth, strength and stability of the clot that is formed. Analysis of the stability and strength of the clot formed provide information regarding the ability of the clot to perform the work of haemostasis. The kinetics of clot formation determines the adequacy of various quantitative factors that are available for clot formation which can be measured. Therefore TEG can measure various aspects of haemostasis such as the life of a clot in vitro, time taken to formation of the initial clot, evaluation of a developing clot in its acceleration and strengthening phases as well as study the phenomenon of clot retraction and clot lysis.

A small venous blood sample (0.36ml) after activation is placed in a prewarmed cuvette. A piston suspended form above is then lowered into the well containing the blood sample. This piston rotates in a 4.5 degree arc backwards and forwards where as in ROTEM the piston is static and the well rotates. Earliest formed fibre strands interact with the activated platelets and attach themselves between the suspended piston and the surface of the cuvette. The movement arising out of the clot formation in the cuvette is transmitted onto the suspended piston. When a "weak" clot forms it can stretch more and can therefore delay the arc movement of the piston. Therefore a clot that is weak will be expressed as a narrow graph on thromboelastography. On the other hand if a strong clot is formed, it will be able to

move the piston proportional to the movement of the well, thereby creating a thick graph on thromboelastography.

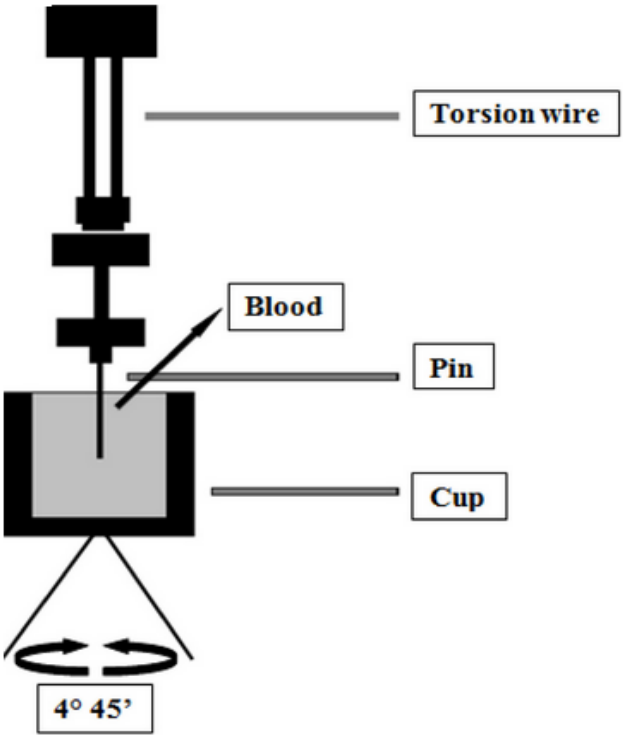


Figure 5: Schematic illustration of the instrumentation utilized in Thromboelastography

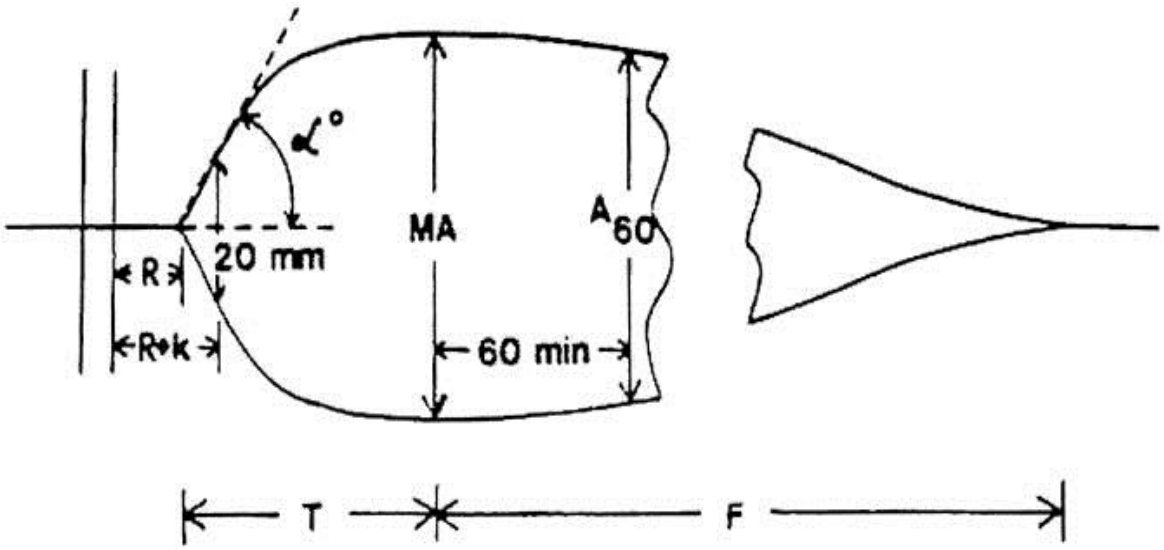


Figure 6: A typical TEG tracing showing the parameters of measurement

The strength of the clot represented over time on a graph shows a characteristic cigar shaped figure.

Parameters of Measurement:

There are mainly five parameters of measurement. They measure different stages of clot development and are as follows:

- **R time:**This is the period of time from initiation of the test to the time of initial fibrin formation.
- **K time:**This is a period of time from beginning of clot formation to time taken for the amplitude of TEG graph to reach 20 mm, and it represents the dynamics of clot formation.
- **Alpha angle:** This is an angle formed between the line in the middle of thromboelastogram and the line tangential to the developing "body" of the thombelastogram. This angle represents the rate of acceleration or kinetics of fibrin cross-linking and build up.
- **MA**–refers to maximum amplitude of the clot formed. It reflects the strength of a clot and is dependent on number and function of platelets and their interaction with fibrin.
- **MA60:** This value measures the rate of amplitude reduction at 60 min. after the MA has been achieved and it represents the stability of the clot.

Clinical interpretation of different stages of coagulation by thromboelastography testing:

- Clot formation:
    - Clotting factors— r, k times
- Clot kinetics:
    - Clotting factors—r, k times

- Platelets—MA

EXAMPLES OF QUALITATIVE TEG TRACES FOR INTERPRETATION:

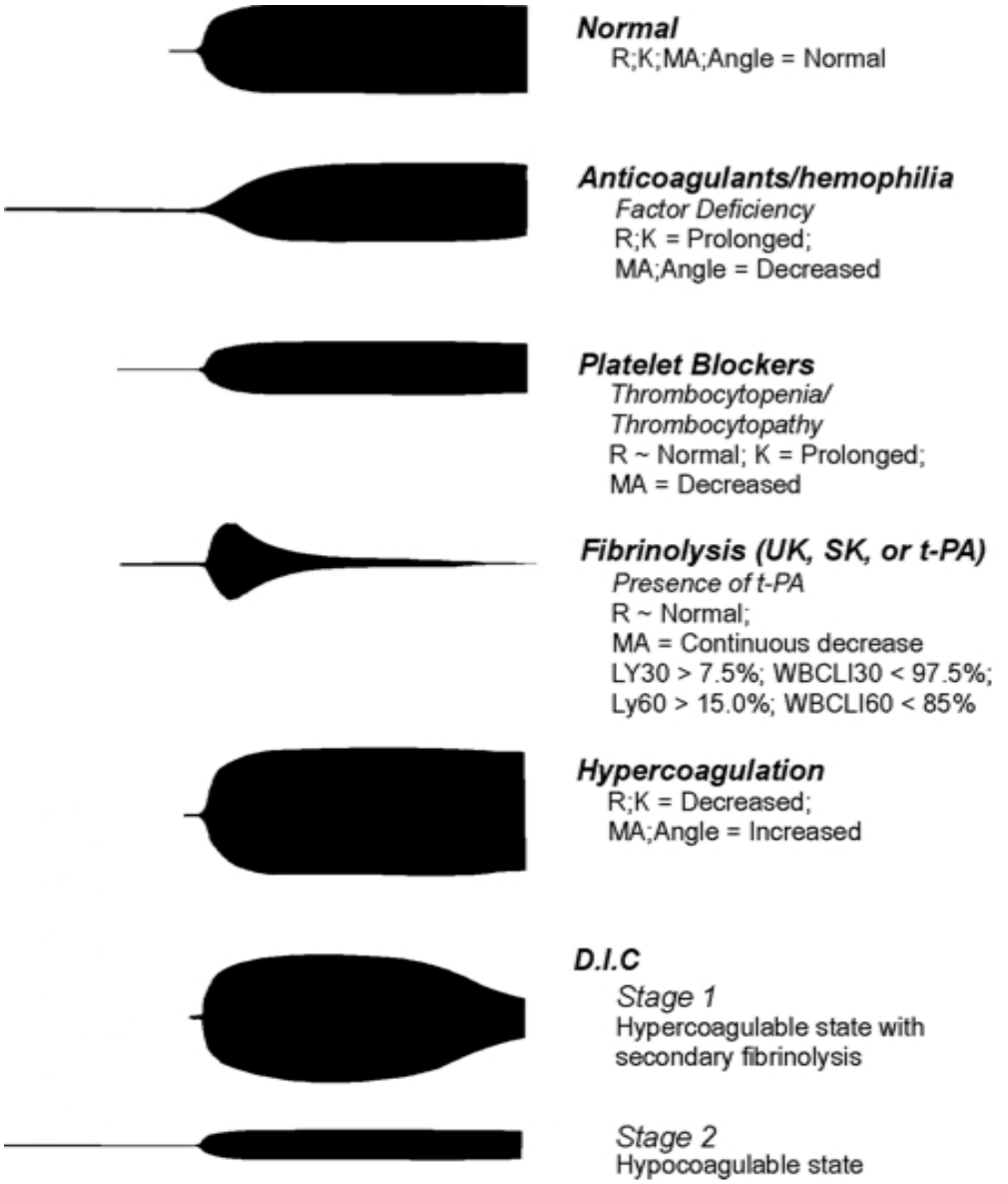


Figure 7: Figure showing various TEG traces for interpretation in specific conditions leading to defects in coagulation.

- Clot strength/stability:
  - Platelets—MA

- Fibrinogen— MA

- Clot resolution:
  - Fibrinolysis—LY30/60; EPL A30/60

Table 1: Correlation between TEG and ROTEM parameters:

TEG Parameters	**ROTEM Parameters**
R time	Clotting Time (CT)
K time	Clot Formation Time (CFT)
Alpha angle	Alpha angle
Maximal Amplitude (MA)	Maximal Clot Firmness (MCF)

The usefulness of thromboelastography has been sufficiently documented in general surgery(70), cardiac surgery(71–73), urology(74), in obstetric patients(75–77), and in liver transplantation(78,79). Probably this is the only test currently that can measure all the steps of clotting in a dynamic way till eventual lysis of the clot or clot retraction occurs. Newer machines are very cost-effective, and this has been demonstrated in several studies.

As far we know, this test namely thromboelastography (TEG/ROTEM) has not been studied as an index of envenomation in patients presenting with snake bite in India. On searching PUBMED and INDMED databases there are noprior studies assessing role of TEG either as predictor of disease severity or for evaluation of coagulopathy in snake bite cases in adults in India.

JUSTIFICATION/RATIONALE FOR THE STUDY

Based on the above observations(52–57,61–66,80) we have postulated that any significant envenomation after a snake bite by any species of snake with have a measurable effect on the clotting process. Inspite of the effect being subclinical at times, this alteration of clotting cascade can be detected by a test of coagulation which does dynamic assessment of the coagulation status such as Thromboelastography (TEG/ROTEM) than the conventional assays regularly used (WBCT/PT/APTT).

This postulate contradicts the conventional wisdom like certain snake venom, particularly venoms causing only neurotoxicity clinically have a single pure action. It is also well established that ischaemic reperfusion injury following tourniquet use itself may be responsible for disturbances of coagulation and considerable toxicity, circulatory instability and metabolic derangement.

Therefore we plan to look at a newer and sensitive test of hemostasis namely thromboelastography to serve as an indicator for identifying envenomation and also as a predictor of severe disease status.

Hadley et al in 1999 have studied TEG among 51 children admitted with snake bite to hospital in Durban, South Africa. They have shown that a normal thromboelastogram could provide assurance that snake envenomation or reperfusion injury secondary to tourniquet has not affected the coagulation status and hence clinically the syndrome is less likely to be severe in nature.(81) The study also concluded that the negative predictive value of TEG, i.e. a normal graph had a better prediction of a milder clinical course when it was compared to other traditional

assays such as prothrombin time and INR.(81) So therefore even though TEG cannot identify the cause of the abnormality, it is understood that it is very good at identifying the abnormalities of clotting process.

Summarising, the proposed study aims to see that in developing countries such as India where there is almost nil availability of specific and rapid venom detection kits for widespread use after a common problem such as snake bite, if any of the tests of coagulopathy including newer tests such as thromboelastography can be useful as predictors of clinical outcome.

MATERIALS AND METHODS

SETTING:

The study was conducted among the patients presenting to the Emergency department and Department of General Medicine of Christian Medical College Vellore Hospital with features of snake envenomation.

Christian Medical College Vellore is a tertiary level hospital providing health services to the population of Vellore city in the state of Tamil Nadu. It is 2500 bedded hospital with a daily outpatient attendance of more than 6,500 patients every day. Around 80 – 100 snake envenomation's are seen every year in the Emergency Department of the hospital. This study was conducted in the department of Emergency Medicine, General Medicine and Clinical Pathology for a period of 18 months.

Sequentially encountered patients with snake envenomation were recruited after taking written informed consent and were followed up till discharge with a clinical research form. Every patient was subjected to a 20 min whole blood clotting time (20min WBCT) test at admission. Additional two citrated samples of 3 ml whole blood were taken at admission and 6 hours later from the patient along with the routine blood samples.

The acute management of patients was provided by the Department of Accident and Emergency. Later the patients were admitted to the medical wards or ICU depending on the severity where they were followed up till discharge. The patients are mostly from the lower and middle socio-economic strata and are mostly from Tamil Nadu and Andhra Pradesh.

DETAILS OF STUDY DESIGN:

- **Study type:** Analytical study
- **Study design:** Prospective observational Cohort study with nested case control design. It involved observation and obtaining data from adult patients with snake envenomation and follow up of this cohort of patients till discharge. The cohort was divided into patients with mild to moderate envenomation and severe envenomation according to snake bite severity score by Dart et al and comparison of various factors was made to predict severe envenomation
- **Type of comparison group:** Internal comparison
- **Duration of the study:** The study was conducted between November 2012 and August 2014 on a prospective basis. The recruitment phase spanned over an 18 month period from January 2013 to June 2014. The total period of study including analysis and write was 21 months.

PATIENTS:

Study population: All patients admitted to Christian Medical College Hospital Vellore during the period January 2013 to June 2014, with history of snake bite having noticed the offending snake and patient with doubtful history of snake bite but with definite acute onset of symptoms and signs of local systematic envenomation without any other causes for the same. We included those who consented to participate after careful exclusion criteria.

Patients were recruited principally under 2 clinical categories:

1. Patients with mild/moderate severity of snake envenomation
2. Patients with high severity of snake envenomation.

Sources of information:

1. Study participants interview
2. Hospital records examination
3. Laboratory testing results.

Inclusion criteria:

1. Age more than 15 years
2. Newly presenting to the emergency department with alleged history of snake bite with features of snake envenomation like local bite site reaction, hemotoxicity or neurotoxicity.

Exclusion criteria:

1. Age less than or equal to 15 years.
2. Pregnant women
3. Patients with known haematological disorders or malignancies that may affect the coagulation pathway.
4. Patients on known anticoagulant or antiplatelet medications.
5. Patients with known history of chronic liver disease.
6. Patient refusing to give consent to be part of the study.

Outcome measures:

Primary outcome: Sensitivity and Specificity of Thromboelastography in assessing disease severity in patients with snake envenomation.

Secondary outcomes:

1. To determine the severity of snake envenomation based on Snake bite severity score.
2. To determine the demographic, clinical and laboratory risk factors predicting high disease severity in patients with snake envenomation.
3. Sensitivity and Specificity of Thromboelastography in assessing coagulopathy in patients with snake envenomation
4. To assess the role of TEG in identification of platelet abnormalities.
5. To assess the role of Thromboelastography in identification of low fibrinogen levels

PROTOCOL IMPLEMENTATION

Step 1 Recruitment:

All patients who fulfilled the inclusion criteria were recruited by the principal investigator after obtaining a written consent (annexure 1). Details on demography, time of bite, environment setting, clinical deficits, presentation to hospital, risk factors, imaging findings, investigations, course of hospital stay and treatment taken were obtained and recorded in the clinical research form (annexure 2). Each patient underwent the severity estimation of snake envenomation by the Snake Bite Severity Score by Dart et al which was

administered to the patients by the principle investigator at the time of recruitment. Patients recruited were categorized according to the severity type of snake envenomation (Mild to moderate envenomation: score <8, Severe envenomation: score>=8) based on the score obtained by the above mentioned scoring system. The researcher did not interfere with the management or the investigations that were ordered for each patient during their entire hospital stay.

Step 2: Data collection

A history and physical examination was done for all recruited patients at the time of enrolment. The following data were collected in data extraction forms for all recruited patients. (Annexure 2)

1. Baseline demographics – age, sex, place of residence, date of admission, time of admission and mode of transport.
2. Details of onset of symptom and presentation: Time of snake bite, time of first medical contact after the snake bite, time of presentation to CMC after the snake bite, details of first aid including the type of first aid received and details of Anti Snake Venom received.
3. Details of Snake Envenomation:
    a. Site of the snake bite
    b. Features of local envenomation including presence of cellulitis, local pain, necrotising fasciitis, compartment syndrome and local bleeding
    c. Features of hemotoxicity including bleeding gums, epistaxis, hematemesis, haematuria, intra-abdominal/intracranial bleed and details of blood transfusions.

d. Features of neurotoxicity including ptosis, opthalmoplegia causing diplopia, cranial nerve palsies, breathing difficulty with paradoxical respiration requiring ventilation.

e. Features of nephrotoxicity including rise of creatinine, requirement of dialysis.

f. Features of rhabdomyolysis including rise of creatinine phosphokinase.

4. Assessment of risk factors :

1. Timing of bite
2. Environment in which snake bite occurred.
3. Usage of footwear.

5. Scoring Systems:

Clinical severity of the snake envenomation was assessed by *Snake bite severity score* by Dart et al. The Snakebite Severity Score (SSS) is a validated and objective scale to assess severity of envenomation including six body categories: local wound, pulmonary, cardiovascular, gastrointestinal, hematologic, and nervous system effects. The total score ranges from 0-20. The score correlated with physician assessment at initial patient presentation ($r = 0.63, Z = 6.52, P < 0.000001$).

Criterion	Points
Pulmonary system	
No symptoms/signs	0
Dyspnea, minimal chest tightness, mild or vague discomfort, or respirations of 20 to 25	1
Moderate respiratory distress (tachypnea, 26 to 40 breaths/minute; accessory muscle use)	2
Cyanosis, air hunger, extreme tachypnea, or respiratory insufficiency/failure	3
Cardiovascular system	
No symptoms/signs	0
Tachycardia (100 to 125 beats/minute), palpitations, generalized weakness, benign dysrhythmia, or hypertension	1
Tachycardia (126 to 175 beats/minute) or hypotension, with systolic blood pressure greater than 100 mm Hg	2
Extreme tachycardia (>175 beats/minute), hypotension with systolic blood pressure <100 mm Hg, malignant dysrhythmia, or cardiac arrest	3
Local wound	
No symptoms/signs	0
Pain, swelling, or ecchymosis within 5 to 7.5 cm of bite site	1
Pain, swelling, or ecchymosis involving less than half the extremity (7.5 to 50 cm from bite site)	2
Pain, swelling, or ecchymosis involving half to all of extremity (50 to 100 cm from bite site)	3
Pain, swelling, or ecchymosis extending beyond affected extremity (more than 100 cm from bite site)	4
Gastrointestinal system	
No symptoms/signs	0
Pain, tenesmus, or nausea	1
Vomiting or diarrhea	2
Repeated vomiting, diarrhea, hematemesis, or hematochezia	3
Hematologic symptoms	
No symptoms/signs	0
Coagulation parameters slightly abnormal: PT, <20 seconds; PTT, <50 seconds; platelets, 100,000 to 150,000/mL; or fibrinogen, 100 to 150 μg/mL	1
Coagulation parameters abnormal: PT, <20 to 50 seconds; PTT, <50 to 75 seconds; platelets, 50,000 to 100,000/mL; or fibrinogen, 50 to 100 μg/mL	2
Coagulation parameters abnormal: PT, <50 to 100 seconds; PTT, <75 to 100 seconds; platelets, 20,000 to 50,000/mL; or fibrinogen, <50 μg/mL	3
Coagulation parameters markedly abnormal, with serious bleeding or the threat of spontaneous bleeding: unmeasurable PT or PTT; platelets, <20,000/mL; or undetectable fibrinogen; severe abnormalities of other laboratory values also fall into this category	4
Central nervous system	
No symptoms/signs	0
Minimal apprehension, headache, weakness, dizziness, chills, or paresthesia	1
Moderate apprehension, headache, weakness, dizziness, chills, paresthesia, confusion, or fasciculation in area of bite site	2
Severe confusion, lethargy, seizures, coma, psychosis, or generalized fasciculation	3

PT, prothrombin time; **PTT,** partial thromboplastin time.
Points are assessed on the basis of manifestations caused by the venom itself (antivenom reactions not included). Ranges given are for adults; appropriate compensation should be made for age.

Ref : Dart RC, Hurlbut KM, Garcia R, Boren J. Validation of a severity score for the assessment of crotalid snakebite.(82)

6. Quantitative variables:

F1: Clinical parameters:

1. Blood pressure
2. Heart rate/rhythm abnormalities
3. Respiratory rate
4. GCS score
5. Pallor and Icterus

F2: Laboratory parameters:

1. Glucose levels (by glucometer)
2. Temperature (by thermometer)
3. Oxygen saturation (by pulse oximetry)
4. Complete blood count including platelet count (by automated coulter counter)
5. Serum electrolytes (by automated chemistry analyser using ion selective electrodes)
6. Prothrombin time with International Normalised Ratio [PT with INR] (by automated coulter counter)
7. Activated Partial Thromboplastin Time [APTT] (by automated coulter counter)
8. Thromboelastography(TEG) / Rotational Thromboelastometry(ROTEM)
9. Serum Fibrinogen Level
10. Liver Function Tests (by automated chemiluminiscence assay)
11. Serum Creatinine (by automated chemistry analyser using calorimetric method)
12. Serum Lactate Dehydrogenase (by chemiluminiscence assay)

13. TEG/ROTEM: sample was obtained at admission and if normal was repeated 6 hours later. (Kindly refer to standard operating procedures (SOP) attached in appendix 3a).

7. Normal Values

    a) Normal TEG(ROTEM) parameters

        CT(Clotting Time): 324 – 565 (seconds),

        CFT(Clot Formation Time) 112 – 224(seconds),

        Alpha Angle: 50 – 68 (degree),

    MCF(Maximum Clot Firmness) : 55 – 66 (mm)

    b) Prothrombin time is considered prolonged if INR > 1.2

    c) Whole blood clotting time > 20 min is considered prolonged.

    d) Activated partial thromboplastin time is considered prolonged if > 34 sec

8. Definitions:

SNAKE BITE DEFINITION: (any of the following)

1. Patient presenting with history of snake bite with
    a. snake seen by patient or bystanders *or*
    b. snake brought along with the patient to the hospital
    c. Circumstantial evidence of snakebites, having noticed the snake but could not be identified.
    d. By identification of the snake from the photographs
    e. By the description given by the patient about the snake's length, thickness, colour, head etc
    f. By the development of signs and symptoms of local or systematic

envenomation

g. Patients with fang marks-Two puncture wounds were taken as due to poisonous snake and inverted 'U' shaped or multiple teeth marks were taken as non-poisonous

2. Unknown bite with characteristic clinical envenomation responding to Anti Snake Venom therapy.

DEFINING ENVENOMATION TERMS:

1. Non-venomous bite :
    a. No signs of envenomation after a period of 24 hour observation in the hospital emergency department.
2. Local envenomation: (any of the following)
    a. Local swelling in the absence of a tourniquet
    b. Enlarged tender lymph node draining the bitten limb
    c. Cellulitis, Necrosis, Blistering
    d. Necrotising fasciitis
    e. Compartment syndrome –absent pulses.
3. Haemotoxicity:
    a. Characteristic hemorrhagic manifestations (either local or systemic bleed) *or*
    b. Whole blood clotting time › 20 minutes *or*
    c. Deranged PT/PTT
4. Neurotoxicity- (any of the below)
    a. Ptosis *or* Opthalmoplegia
    b. Limb muscle weakness grade 4 *or* less
    c. Respiratory paralysis-paradoxical breathing / Type 2 respiratory failure

d. Respiratory failure requiring need for intubation

5. Definition of Renal failure – KDIGO 2012 guidelines : (any of the below)

   a. Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 micromol/L) within 48 hours
   b. Increase in serum creatinine by ≥1.5 times baseline, which is known or presumed to have occurred within the prior seven days
   c. Urine volume <0.5 mL/kg/h for six hours

6. Definition of Rhabdomyolysis: Creatinine phosphokinase levels > 195 U/L.

Step 3 Follow Up

All patients of snakebite were carefully monitored during hospital stay till discharge to find out development of any further complications or new symptoms and signs. Each patient was followed up till discharge and details such as ASV requirement, Clinical course (improved or deceased), development of complications, and requirement of blood products, dialysis, ventilation or any surgical procedure for compartment syndrome were assessed.

MEASURES TO REDUCE POTENTIAL BIAS

As this was an observational study only, the patient management was not be influenced by the study. Recall bias was the other bias that was anticipated to occur during the collection of the exposure variables (with respect to past history). All attempts were taken to minimize this bias by trying to procure evidence in the form documentation, wherever possible, for the history given by the participants. Other possible sources of bias include:

a) Method of blood collection.

b) Bias during performing the laboratory tests.

c) Assessment of disease severity with questionnaire.

SAMPLE SIZE CALCULATION:

A detailed scientific literature review was done in the Pubmed and Indmed databases to identify studies done to determine the role of thromboelastography (TEG) in patients with snake envenomation. Hadley et al in 1999 have shown in 51 children admitted with snake bite to hospital in Durban, South Africa that normal TEG provides assurance that envenomation or reperfusion has not affected the clotting cascade and therefore the clinical syndrome is unlikely to be severe. They also showed that normal TEG has a better predictive value for a benign clinical course as compared to traditional clotting assays such as INR.(81)

Therefore the sample size was calculated based on the following assumptions**.** The **sensitivity of TEG in assessing disease severity was expected to be 95%** and **specificity was expected to be 45%**.(68) Different levels of precision were assessed and at a precision of ±5 and ±15 for sensitivity and specificity respectively, a total sample size of **76** was calculated.

Sensitivity	**Precision**	**Sample size**
95	2	200
95	4	118
95	5	76

Specificity	Precision	Sample Size
45	5	395
45	10	100
45	15	44

STATISTICAL ANALYSIS:

The data collected was entered with Microsoft Office EXCEL software following which statistical analyses were performed using *STATA (DATA analysis and statistical software)* version **13.00** for Windows 97 and above. Continuous variables were summarized as mean with standard deviation or median with maximum and minimum values of the ranges. The categorical variables were summarized as numbers and percentages. Pie charts and bar graphs were used to plot single variables. The chi – square test was used for comparison of categorical variables. Odds ratios (OR) and confidence intervals (CI) were calculated and a 'p' value less than .05 was considered statistically significant. All reported p values are two sided.Diagnostic accuracy measures with 95% CI (Sensitivity, Specificity, Positive predictive value and Negative predictive value) were calculated for 20 minute whole blood clotting time, Prothrombin time, activated partial thromboplastin time and Thromboelastography. Logistic regression methods were used to assess factors associated with poor clinical response. All analysis were done using the STATA software version 13.0 (STATACORP, TEXAS) and Microsoft EXCEL for data entry.

Funding:

The expenditure for the entire study was borne by the institution through a grant allotted by the institutional review board for this specific purpose.

Institutional Review Board Approval (IRB) and Ethical considerations:

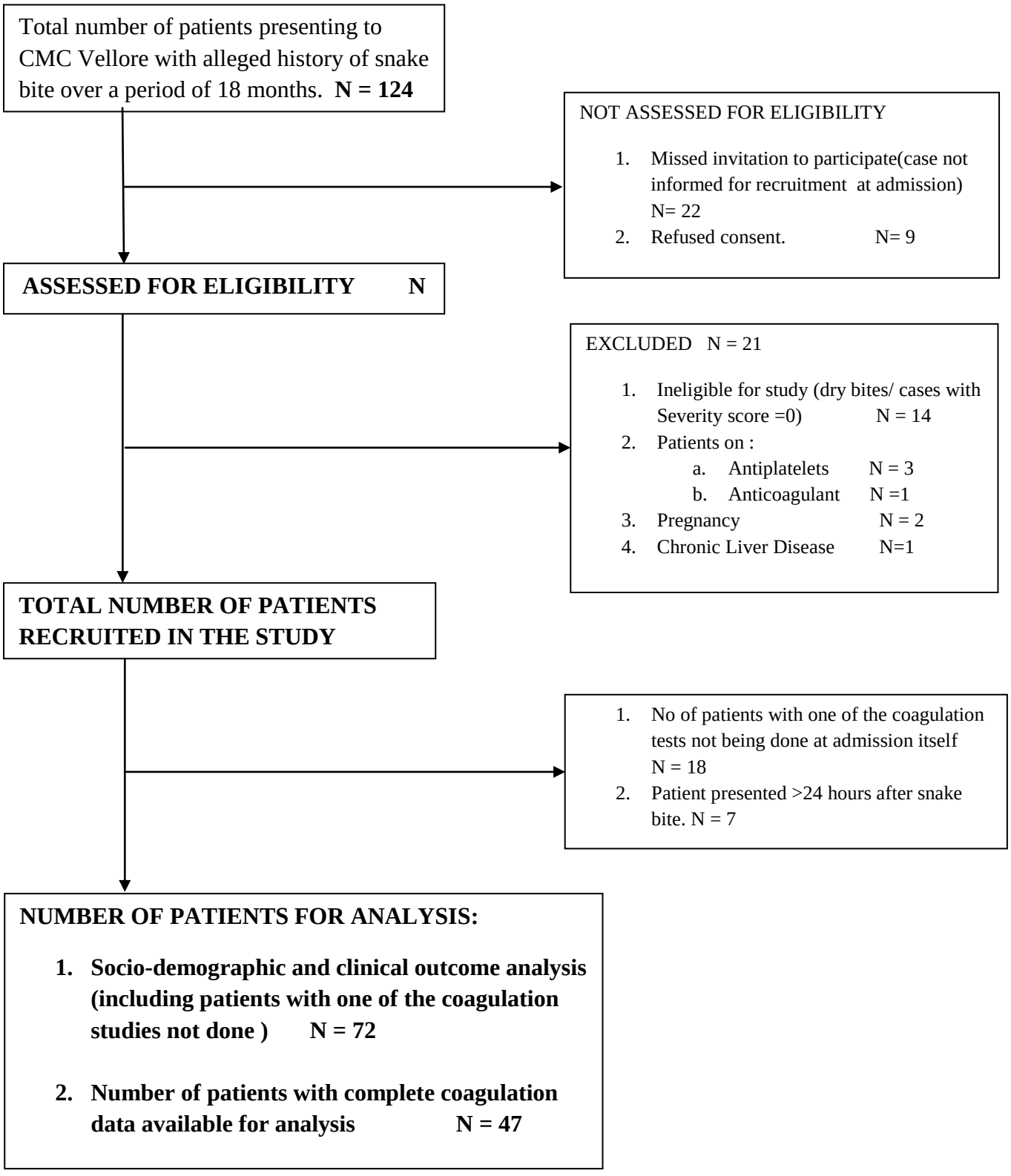
Institutional review board approval was obtained prior to the commencement of the study. [IRB study approval number: 8037 dated 01.10.2012].

The IRB approval form has been attached at the starting of this document.

RESULTS

The study was carried out in the Emergency department and the Medical wards of Christian Medical College Hospital, Vellore between January 2013 and June 2014.

Figure 8: STROBE Figure–Flow of patients into the study



A total of 124 patients with newly diagnosed case of snake envenomation, above the age of 15 presented to the emergency department. 22 patients missed invitation to participate at admission and 9 patients refused consent to take part in the study. Hence the remaining 93 patients were assessed for eligibility. 21 patients were further excluded due to various reasons after assessing for eligibility (14 patients had dry bites, 3 were on antiplatelet medication, 1 patients was on anticoagulation, 2 patients were pregnant, 1 patient had history of chronic liver disease). Of the remaining 72 patients, all of the patients data was included in the descriptive analysis while only those for whom the complete data for coagulation testing was available (i.e. 47 patients) were included in the final statistical analysis.

The Results are presented under the following headings:

1. Analysis of baseline demographic, clinical and laboratory characteristics.
2. Analysis of predictors of severe envenomation.
3. Comparison and analysis of thromboelastography with other coagulation tests.

Analysis of Demographic, Clinical and Laboratory characteristics

DEMOGRAPHIC DETAILS

Total number of patients: 72

Gender distribution of the patients:

There were a total of 53 males (74 %) and 19 females (26 %).The male to female ratio was 2.78.The gender distribution is shown below.

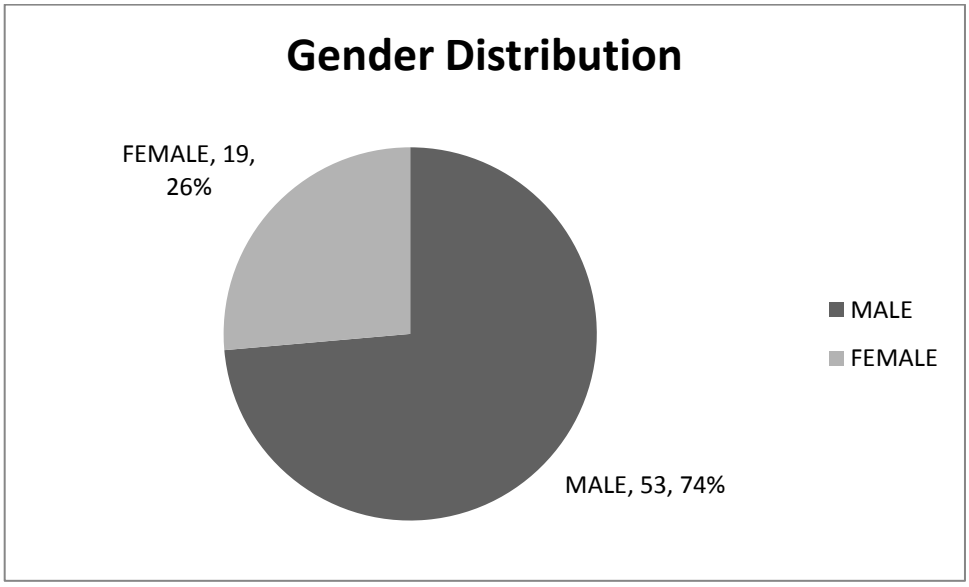


Figure 9: Pie chart showing distribution of patients with snake envenomation based on gender.

Age distribution:

The mean age of the study population was 40.78 ± 13.5 years. The oldest patient was 81 years old while the youngest was 16 years old. The patients recruited were divided into 4 age groups:

1] <20 years of age

2] 21 to 40 years

3] 41 to 60 years

4] >65 years of age.

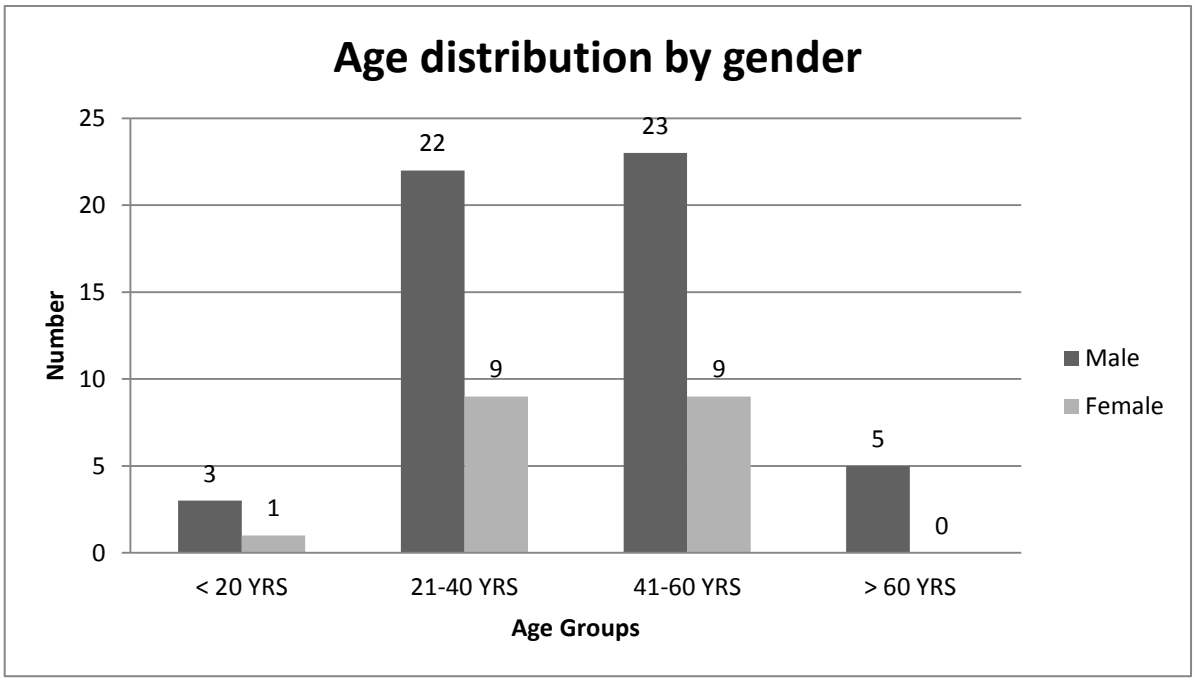


Figure 10: Bar graph showing distribution of patients by age and gender

Males: Snake bites were more common among males and a similar trend was present in all the age groups of <20, 21 – 40, 41 – 60, >60 years of age. While 73.6% of all the patients were males, the maximum number of males with snake envenomation belonged to the age group of 41 – 60(23) closely followed by age group of 21 – 40(22).

Females: Equal numbers of females with snake envenomation were present in the age groups of 21 – 40 and 41 – 60 years which also had the highest number of bites. There was only one case below the age of 20 and no patients in this category above the age of 60 years.

Baseline characteristics:

Table 2: Baseline demographic characteristics of patients at admission.

Characteristic of Patients (N=72)	**Frequency N (%)**
Mean Age	40.78±13.53 years
Male gender	53 (74)
Co- Morbidities	
Diabetes Mellitus	5 (6.9)
Hypertension	4 (5.5)
Smoking	8 (11.1)
Alchohol	4 (5.5)
Coronary Artery Disease	1 (1.3)
First medical contact in hours (Bite to needle time)	2.61 ± 2.01 hours
Duration of Hospital Stay	6.53 ± 4.65 days

The incidence of co morbidities as expected was less as the predominant population was between and 21-60 years old and were among the strong workforce group.

The mean bite to needle time for first medical contact was 2.6 hours with a standard deviation of +/- 2 hours. The minimum time was 0.25 hours (15 min) by a patient who sustained a bite nearby a hospital. The maximum time for first medical contact was 9 hours by a patient who resided in a tribal area over the hills with no primary hospital nearby.

The mean duration of hospital stay was 6.5 day with standard deviation of 4.6 days.

The maximum duration of stay was 24 days and minimum duration was 2 days.

Occupation:

The distribution of various occupations among the patients is as follows:

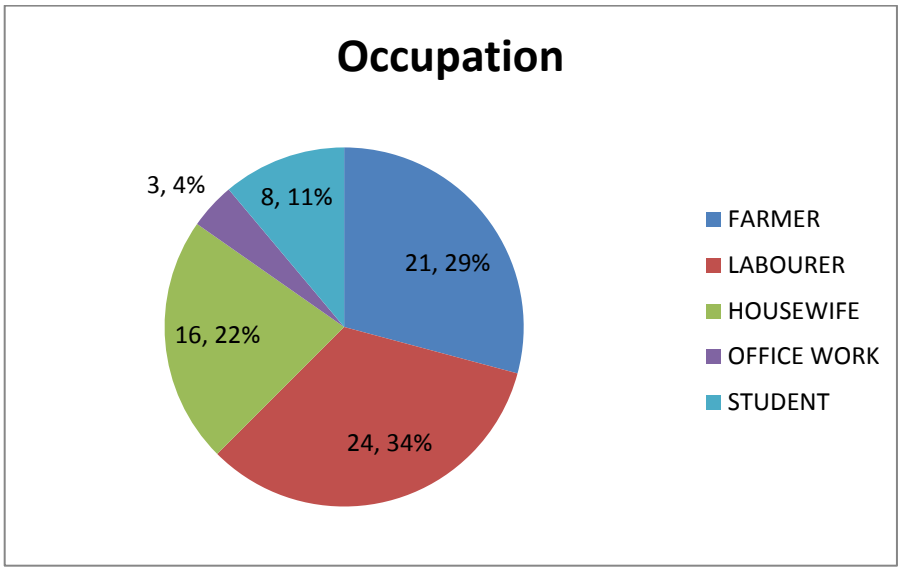


Figure 11: Pie chart showing distribution of patients based on occupation.

The predominant occupation among the study population comprised of farm labourers (34%) and farmers (29%) who together made up more than 60 % of the population.

Most of the females with snake envenomation were housewives (84%, 16/19) who also helped in the farm during the harvest periods.

Region of residence:

Overall 71% [N =51] of study patients were residents of Tamilnadu. The remaining 29% were from Chittoor district in neighbouring state of Andhra Pradesh.

The distribution based on residence is shown below:

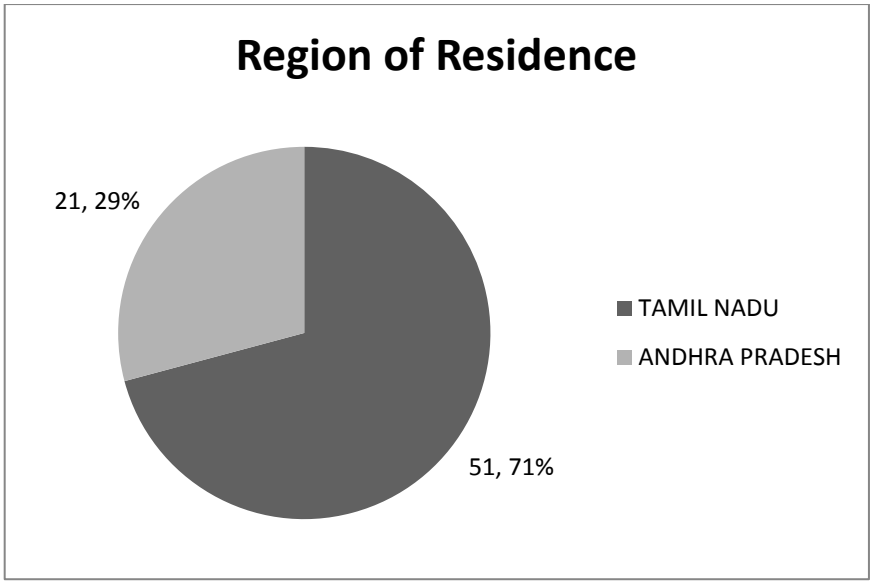


Figure 12: Pie chart showing distribution of patients based on their area of residence

Time of bite:

The maximum number of snake bites occurred in the early morning hours (23 bites) or in the evening hours (22 bites).

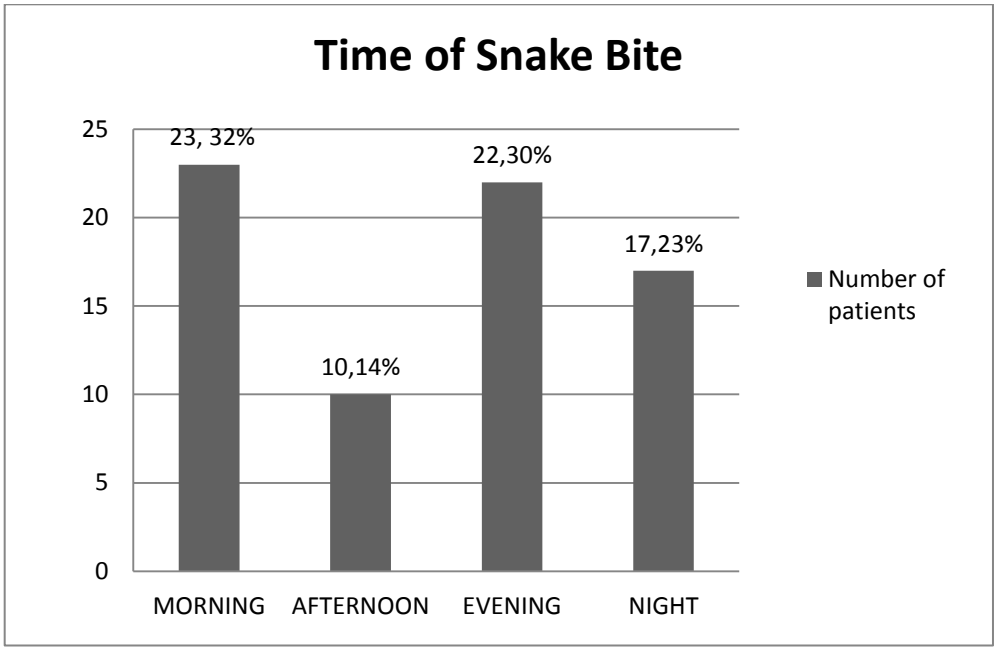


Figure 13: Bar diagram showing the distribution of patients with respect timing of the day during which they sustained the snake bite.

Time elapsed since presentation to the hospital:

57% (N=41) of the patients presented within 6 hours of sustaining the snake bite to the hospital, 10 patients presented between 6 to 12 hours after the bite, 14 patients presented within 12 – 24 hours after the bite. 7 patients had presented after 24 hours of the snake bite.

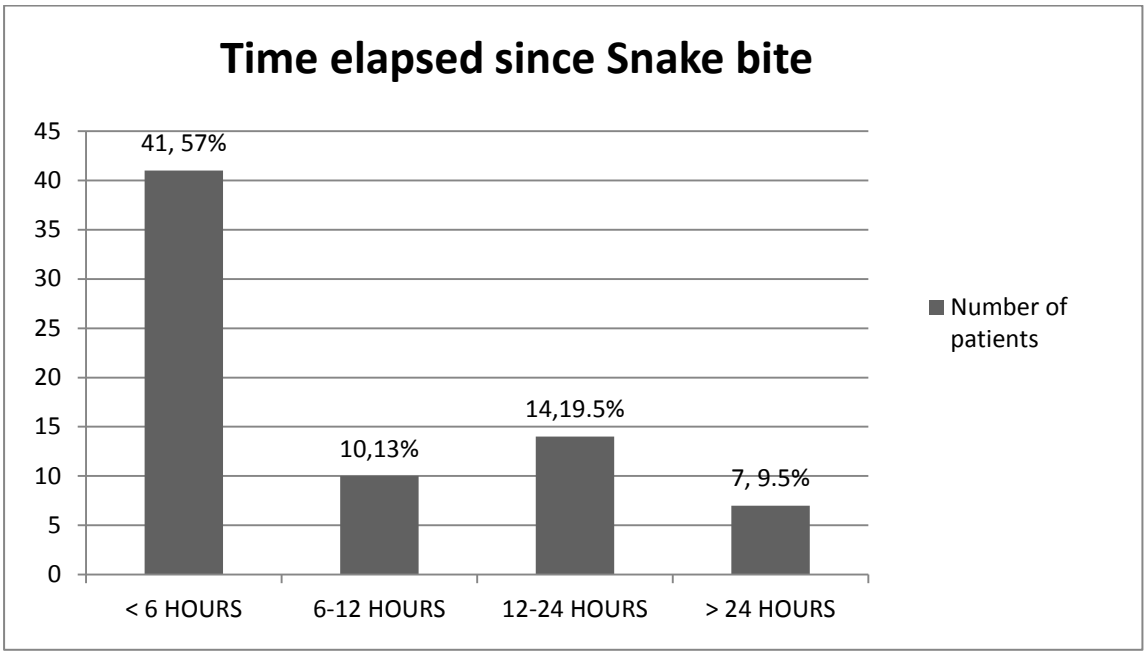


Figure 14: Bar diagram showing the distribution of patients with respect to time elapsed since the bite to presentation to the hospital

Mode of transport:

The predominant mode of transport was the ambulance provided by the government (108 services) which were utilized by 21 patients. 20 patients came by autorickshaw, 16 used four wheelers like cars, 10 used motorcycles and five patients were brought by foot.

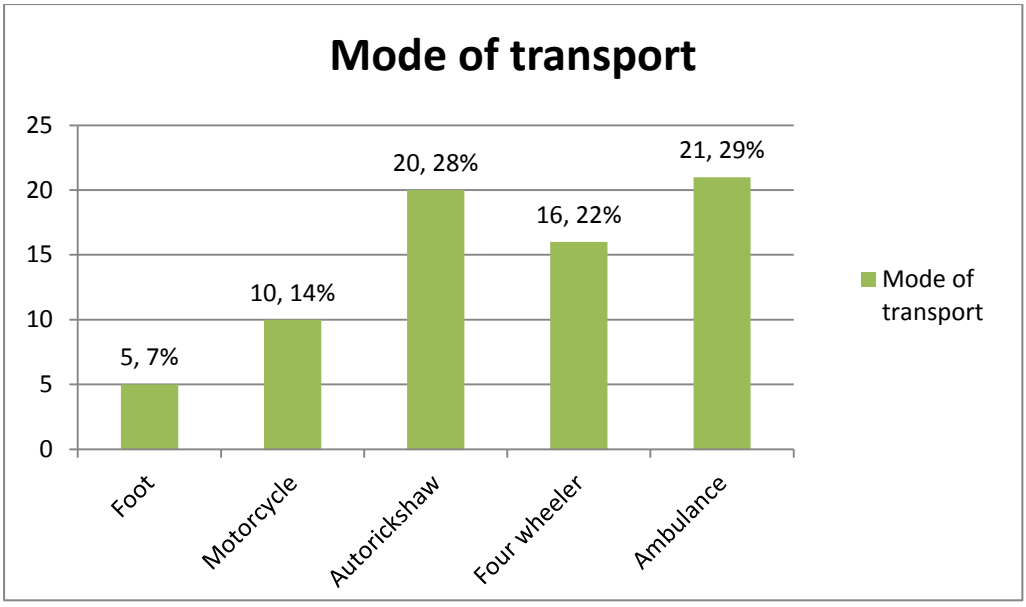


Figure 15: Bar diagram showing the distribution of patients with snake bite describing the mode of transport utilized by them to come to the hospital.

Snake brought with the patient:

The snake was killed and brought along with the patient in 15% of the patient population (11 patients).

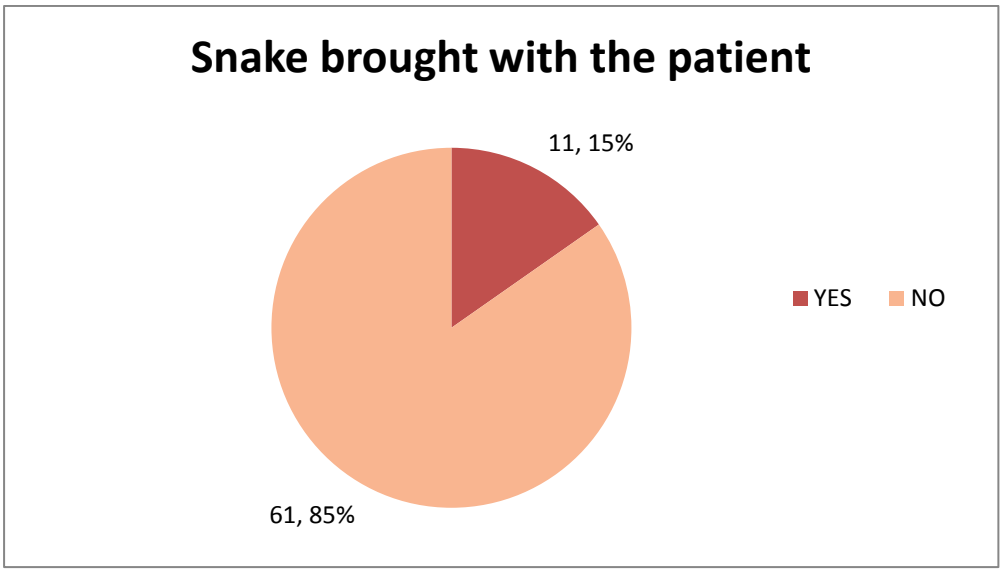


Figure 16: Pie chart showing the number of patients with the snake brought along.

Snake Identification: The type of snake species was identified in about 42% (N=30) of the patient population. The remaining 58% (N=42) were not able to identify the snake bite.

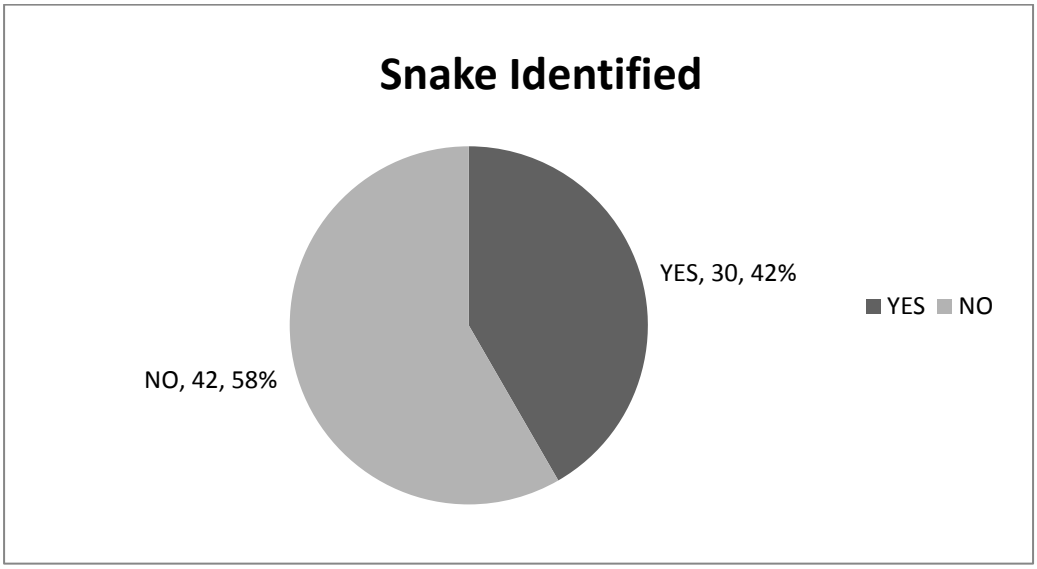


Figure 17: Distribution of patients based on the ability to identify the type of snake species causing the bite.

As stated earlier only 11 patients had killed and brought the snake along with them which we were able to identify. 19 more patients could identify the snake or provide the description of the size, shape, colour, pattern of head and scales based on which assumed the species of snake.

Type of snake species:

Majority of the patients (58%, N=42) could not identify the snake species that had bitten them. Among the identified species the most common species was Russell's viper (31%, N=22) followed by krait (5%). There were 2 cases each of documented Saw scaled viper and Indian cobra.

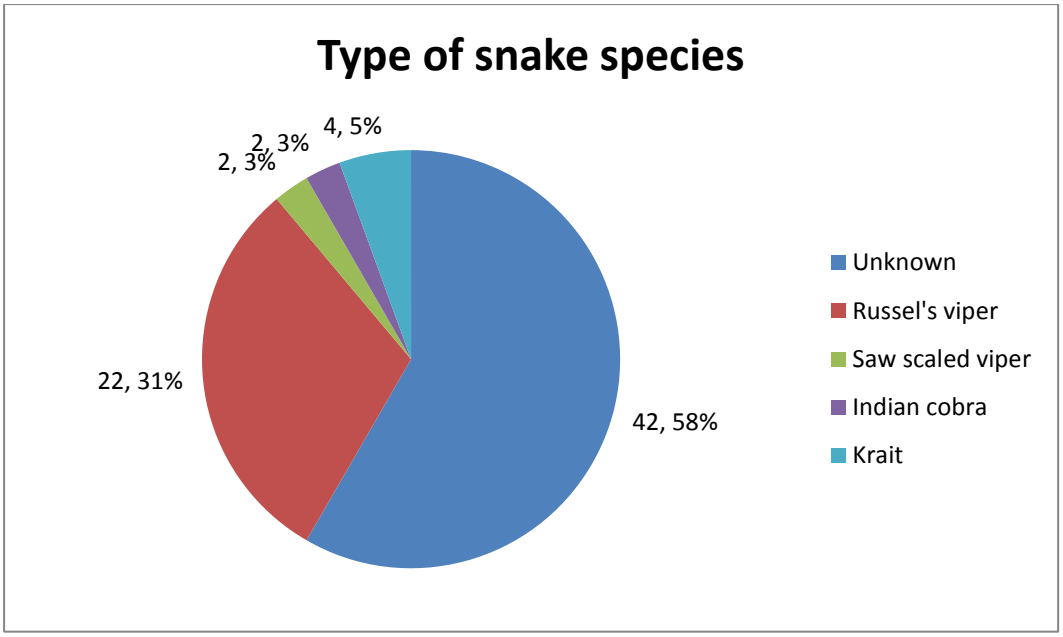


Figure 18: Distribution of patients according to the species of snake that they had been bitten with.

Environmental Setting:

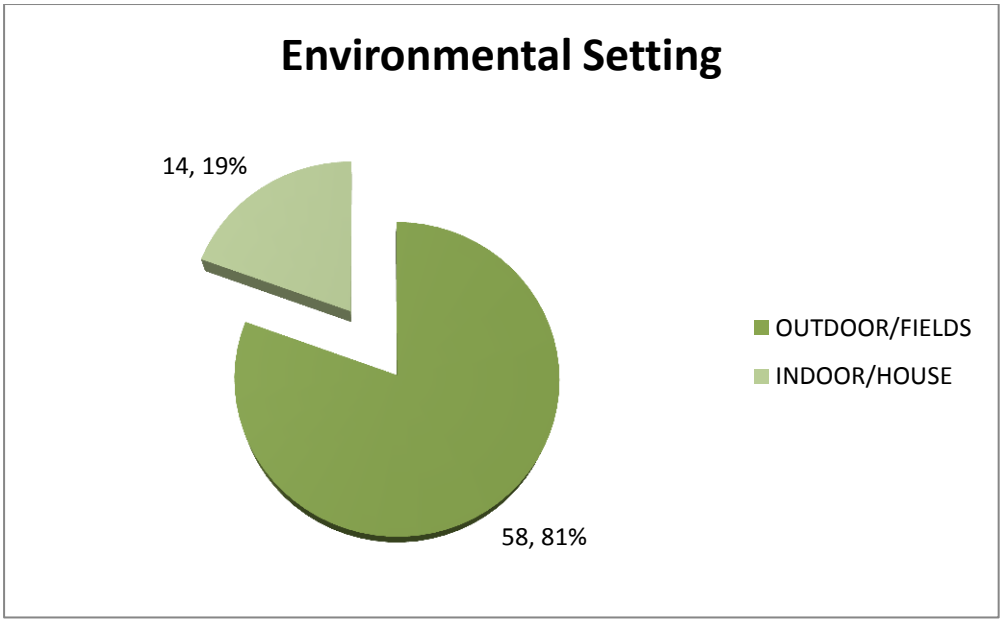


Figure 19: Distribution of patients according to the environmental setting during the time of bite.

CLINICAL PARAMETERS:

Baseline Clinical Parameters:

Table 3: Details of clinical parameters (categorical variables) at admission

Clinical features	Percent	Number of patients (n =72)
Pain at the bite site	90.28%	65
Local swelling	87.50%	63
Fang mark	78%	56
Cellulitis	73.6%	53
Tachypnoea (RR>20/min)	69.44%	50
Neurotoxicity	66.67%	48
Local bleeding	63.89%	46
Ptosis/Opthalmoplegia	54.16%	39
Renal failure	51.39%	37
Vomitng	48.61%	35
Tachycardia(HR>100/min)	36.11%	26
Systemic bleed	34.72%	25
Paradoxical respiration	18.05%	13
Necrotising fasciitis	13.89%	10
Compartment syndrome	8.33%	6

The most clinical feature was pain at the bite sit which was present in 90.28% of the patients followed by local swelling which was seen in 87.5% of the population.

Table 4: Details of clinical parameters (continuous variables) at admission:

Variable	n	Mean	S.D.	Median	IQR
ASV vials received outside	72	6.39	6.25	6	1.5-8
ASV vials received in the hospital	72	11.25	5.98	10	7.5-14
Total ASV vials received	72	17.61	7.71	16	14-20
Heart rate	72	99.57	24.43	97	82-112
Systolic blood pressure	72	115.64	23.34	110	100-125
Diastolic blood pressure	72	73.22	14.04	70	60-80
Saturation (Spo2) at admission	72	94.06	8.45	96	93-98

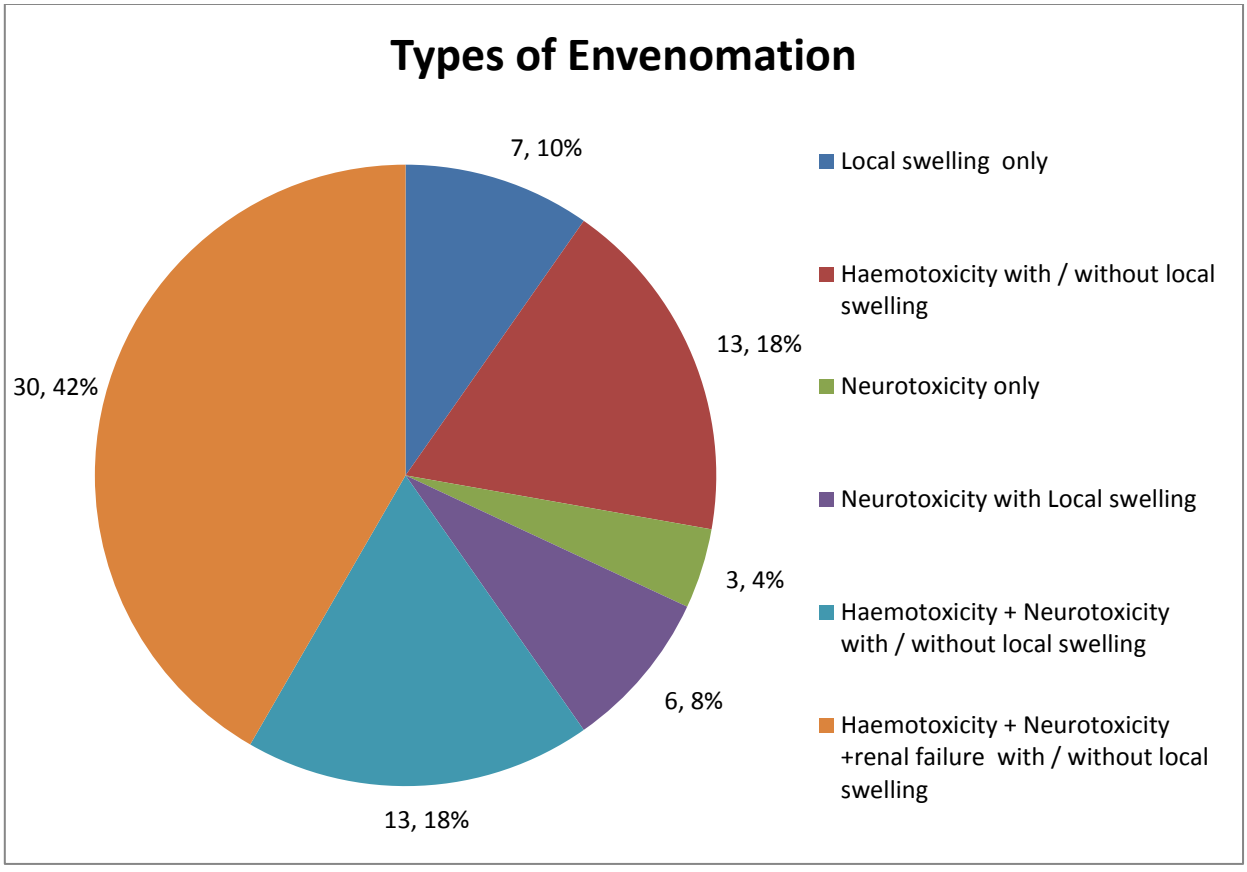


Figure 20: Distribution of patients according to the different clinical syndromes of snake envenomation

Fang Mark:

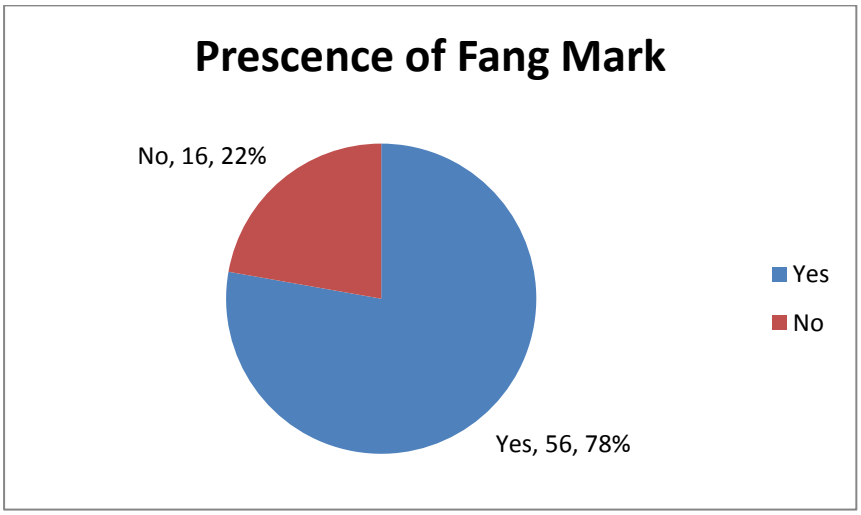


Figure 21: Distribution of patients with respect to presence of fang mark.

Site of Snake Bite:

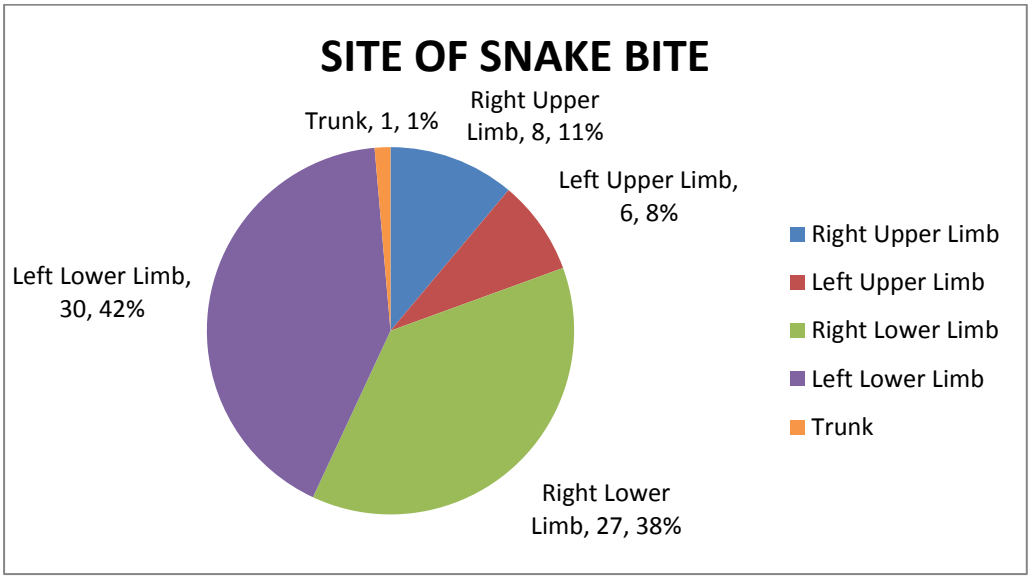


Figure 22: Distribution of patients with respect to the site of snake bite.

Left lower limb with 42% was the most common site of bite among the patients followed by right lower limb with 38%. We had one patient with a snake bite over the anterior abdominal wall which happened when he was sleeping the fields.

Coagulopathy:

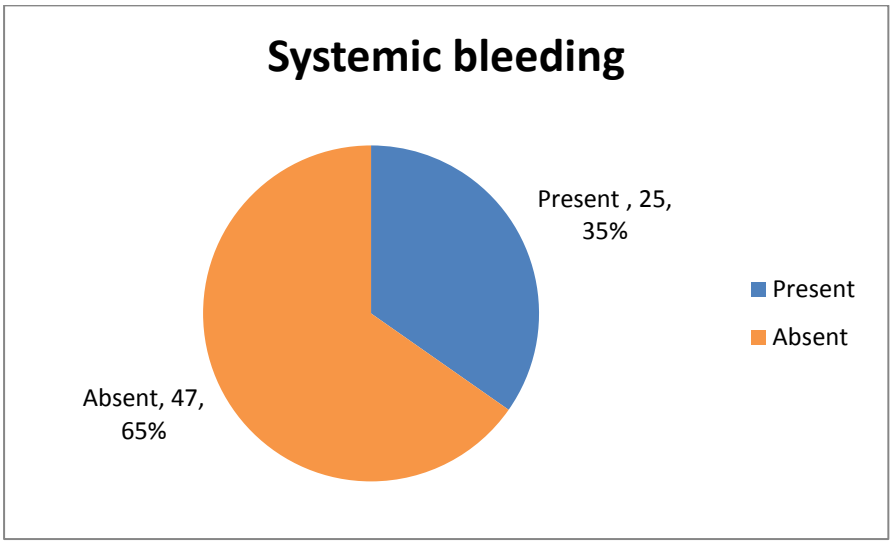


Figure 23: Chart showing the percentage of patients with systemic bleeding among the patients with snake bite.

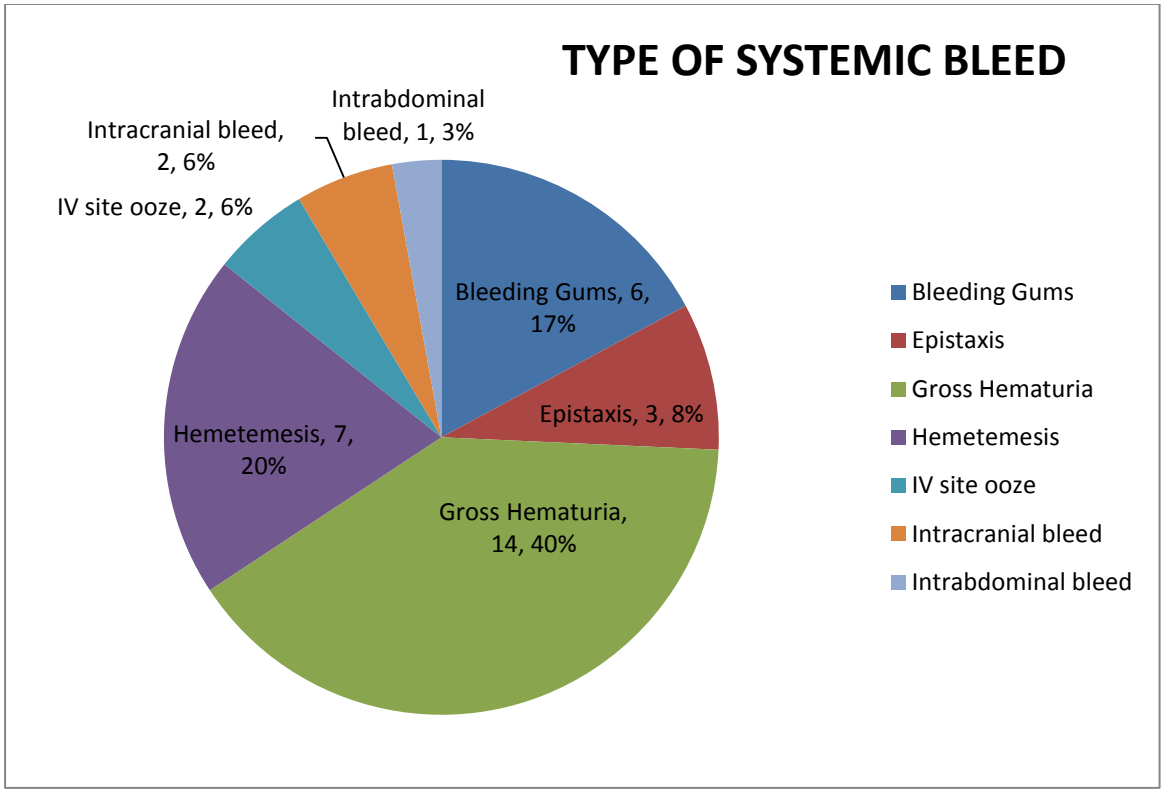


Figure 24: Distribution of various types of systemic bleeding among the patients with systemic bleeding in patient with snake bite.

Neurotoxicity:

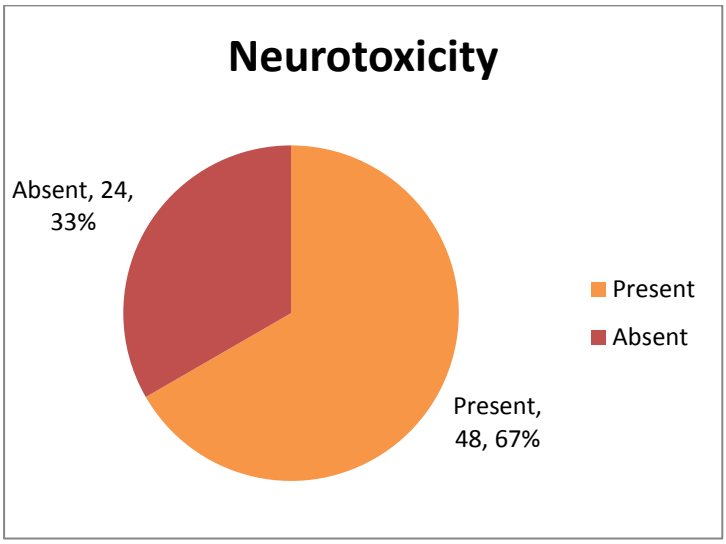


Figure 25: Chart showing the percentage of patients with neurotoxicity among the patients with snake bite.

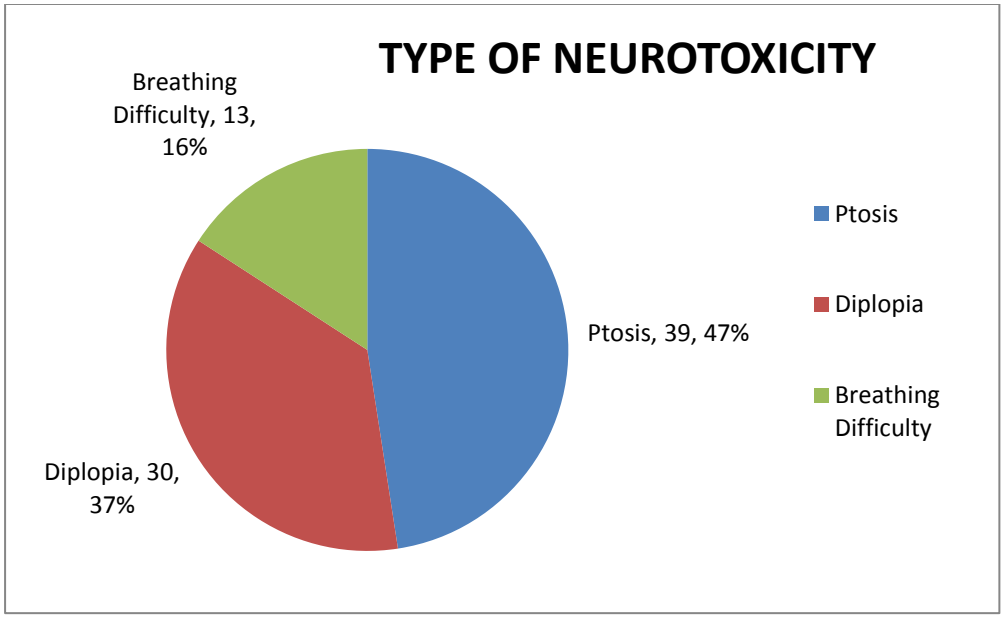


Figure 26: Distribution of types of neurotoxicity among the patients with snake bite.

Predominant neurotoxic features comprised of ophthalmic manifestation which comprised of almost 84% (ptosis was seen in 47% and diplopia in 37%).

LABORATORY PARAMETERS:

Baseline laboratory parameters:

Table 5: Details of laboratory parameters at admission

Variable	**n**	**Mean**	**S.D.**	**Median**	**IQR**
Hemoglobin	72	12.75	2.64	13.15	11.3-14.5
Total Count	71	18050	9791	17500	10120-22000
Platelets	71	169459	106492	175000	74000-253000
Total Bilirubin	45	2.83	3.44	1.6	0.7 - 3.5
Albumin	45	3.64	0.66	3.6	3.1 - 4.2
AST	46	130.37	216.39	56.5	29 – 134
ALT	46	30.41	31.62	19.5	12 – 36
RBS	67	169.57	87.93	146	120 – 190
CPK	57	3236.6	5984.68	913	275 – 3427
LDH	28	1825	1330	1459	759 – 2546
Creatinine	72	27.69	18.32	25.5	11 – 43.5
Urea	67	61.63	55.34	36	26 – 88
Sodium	70	137.74	4.99	139	134 – 141
Potassium	70	12.47	5.98	12	8 – 17
Fibrinogen	17	299	190	320	127 – 446.7
Prothrombin time	72	22.65	20.94	14.75	11.95 - 23.5
INR	72	2.01	1.71	1.40	1.10 – 2.15
APTT	72	40.43	36.06	28.25	25 – 35.3

RBS: Random Blood Sugar, **AST:** aspartate aminotransferase, **ALT:** Alanine aminotransferase, **CPK**: creatinine phosphokinase**, LDH:** Lactate dehydrogenase, **INR**: International Normalized Ratio, **APTT:** Actiated Partial Thromboplastin Time

,

ROTEM PARAMETERS					
Variable	**n**	**Mean**	**S.D.**	**Median**	**IQR**
ROTEM_CT	46	775.63	929.42	399	283 – 860
ROTEM_CFT	41	19.15	11.75	19	9 – 29
ROTEM_A	40	46.35	21.98	46.5	31.5 – 67
ROTEM_MCF	44	42.55	18.62	44	34 - 58
ROTEM_ML	33	9.52	5.56	10	4 - 15

TEG PARAMETERS					
Variable	**n**	**Mean**	**S.D.**	**Median**	**IQR**
TEG_R Time	25	7.53	7.88	3	1 - 14
TEG_K Time	25	10.08	6.30	10	5 - 15
TEG_Angle	25	36.05	21.44	35	23.6 - 55.6
TEG_MA	25	42.02	20.17	44.70	34.8 - 56.3
TEG_Ly30	25	0.04	0.13	0	0 – 0

ROTEM: Rotational Thromboelastometry, **TEG**: Thromboelastography,**CT**: Clotting Time, **CFT:** Clot formation time, **A:** alpha angle, **MCF:** maximal clot firmness, **ML:** Maximal lysis, **MA:** maximal amplitude, **Ly30:** Lysis at 30 seconds.

TREATMENT VARIABLES:

First Aid: 68% (49 patients) received first aid prior to coming to the hospital.

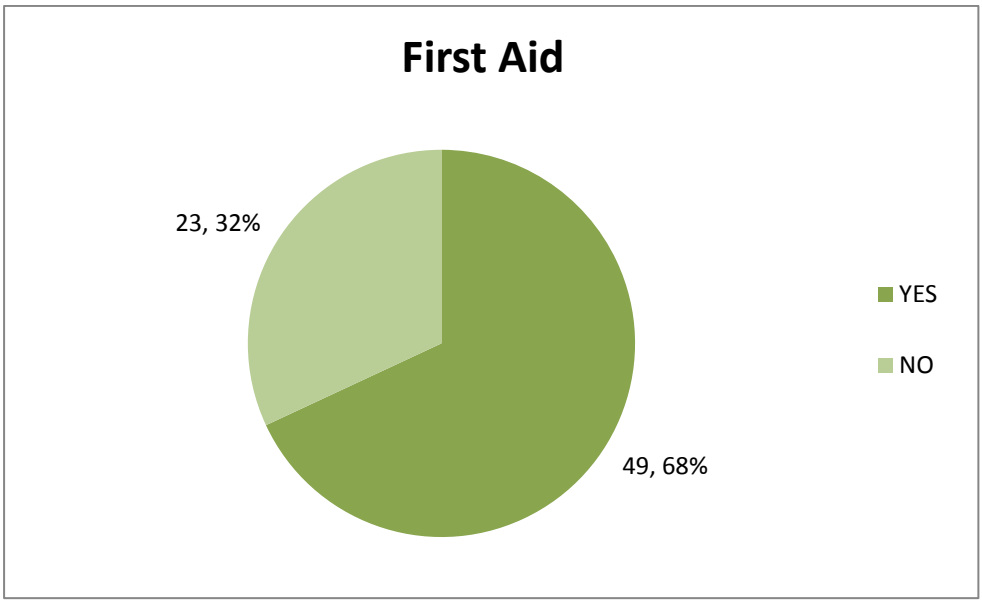


Figure 27: Pie chart showing the distribution of patient with respect to first aid received prior to admission.

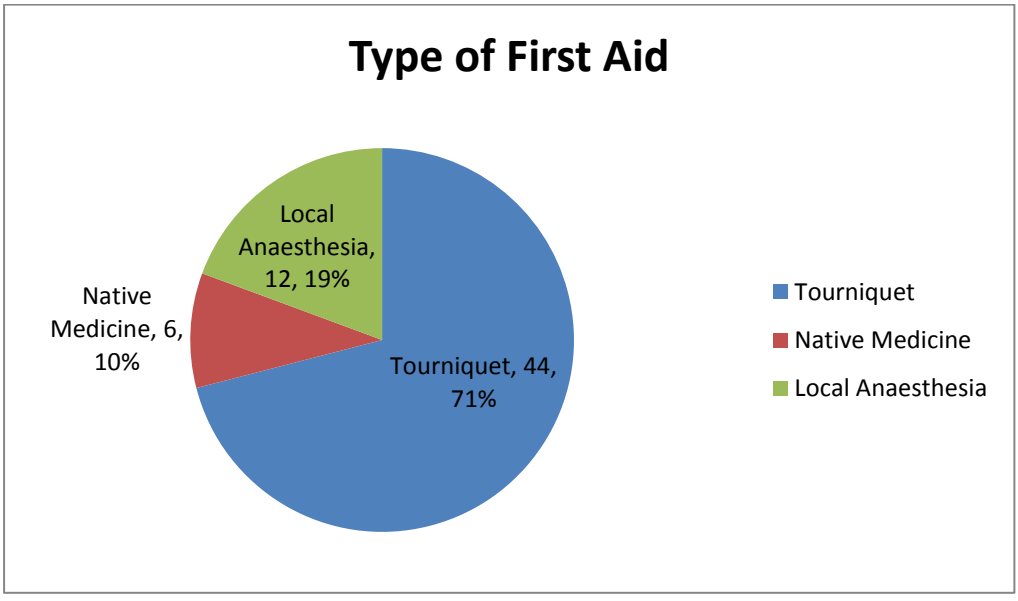


Figure 28: Pie chart showing the distribution of the different types of first aid received prior to admission.

Anti-Snake Venom: 78% of the patient population (56 patients) received ASV at a local centre prior to coming to our hospital. 22% (16) did not receive any ASV prior to admission.

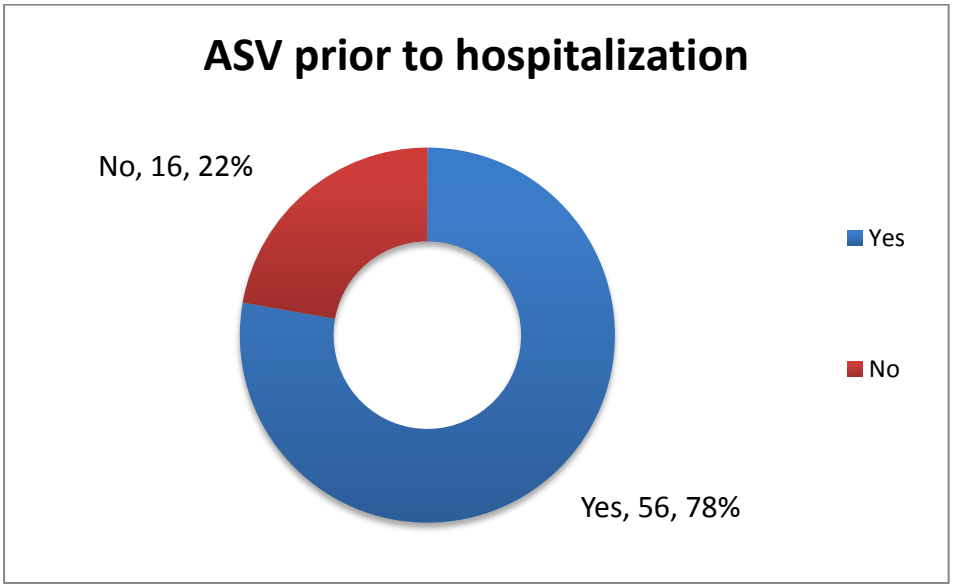


Figure 29: Distribution of patients based on ASV received prior to hospitalization.

Incidence of ASV hypersensitivity:

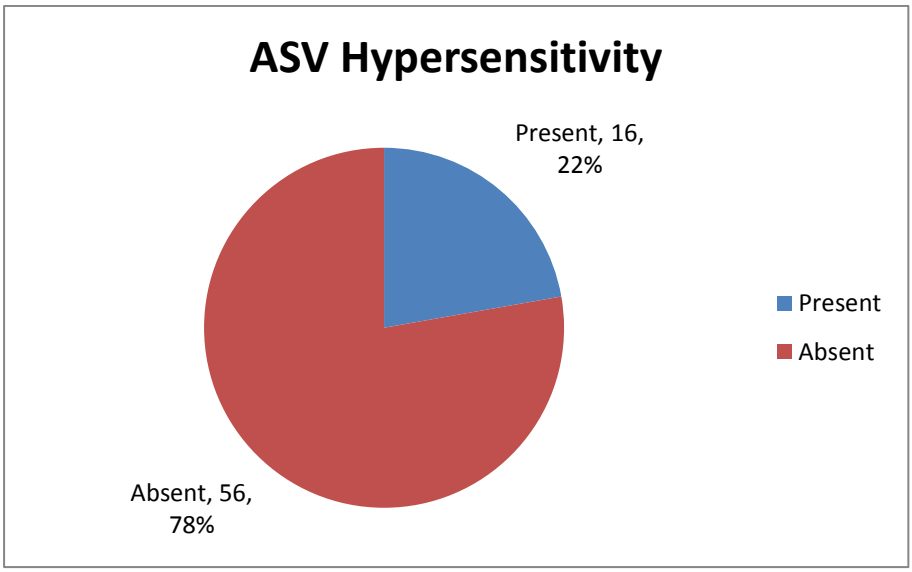


Figure 30: Chart showing the incidence of ASV hypersensitivity among the patients with snake bite.

Type of ASV hypersensitivity:

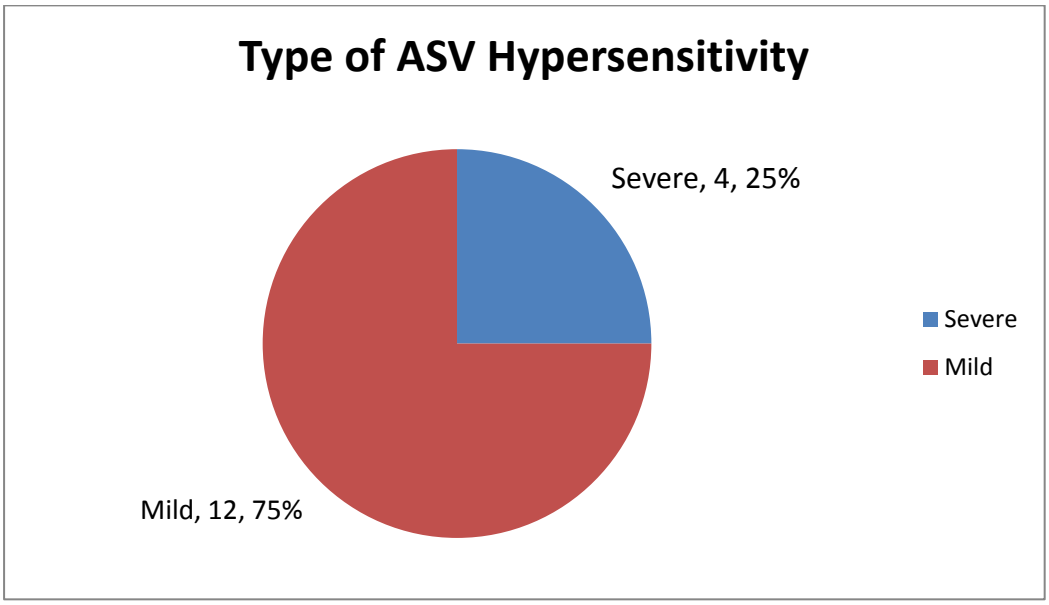


Figure 31: Chart showing the distribution of type of ASV hypersensitivity among patients with Snake Bite who had hypersensitivity to ASV.

Antibiotic Usage: 87.5% (N=63) of the patients received antibiotics during the treatment. The various types of antibiotics used is describes below.

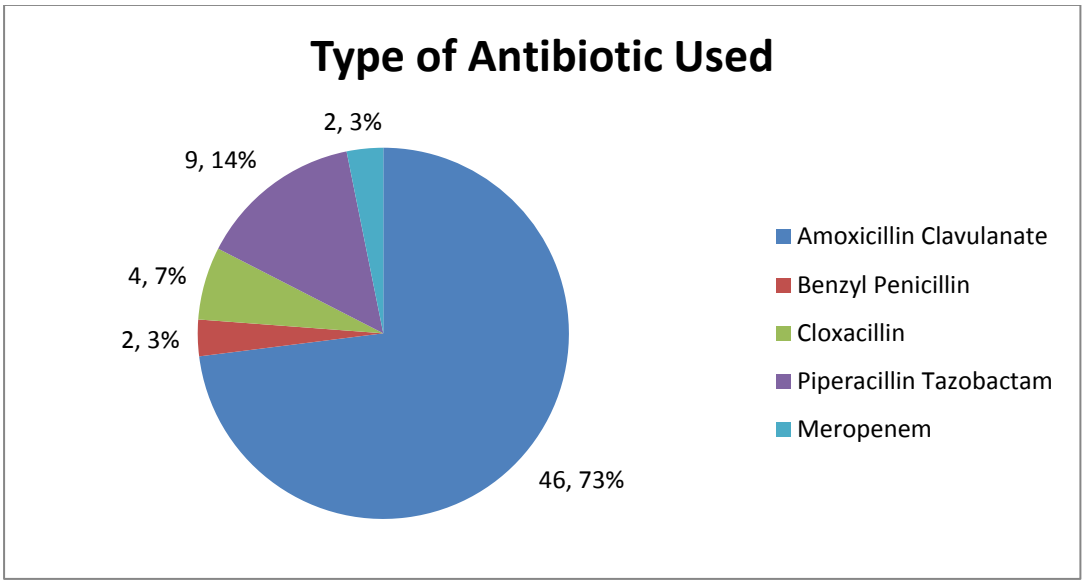


Figure 32: Pie chart showing the distribution of patients with respect to the type of antibiotic used.

Table 6: Treatment details during the admission period

Treatment received	**Percentage (%)**	**N (total =72)**
ASV use	100	72
Antibiotic Use	87.5	63
Mechanical ventilation	18	13
Dialysis	19.44	14
Blood transfusion	16.67	12
Surgical intervention such as fasciotomy/debridement	6.94	5

Mortality:

Table 7: Distribution of cases based on final outcome at discharge

OUTCOME	**N (72)**	**%**
Alive	68	94.5
Dead	3	4.17
Discharge against medical advice	1	1.37

Analysis of Risk factors of Severe envenomation.

Out of the 72 patients that were analysed

- **40 patients (55.5%)** had snake bite severity score of **≥ 8** points suggestive of **severe snake envenomation** clinically at the time of admission.
- **32 patients (44.5%)** had a score of **≤ 7** and were classified as cases of **mild envenomation.**

<u>Demographic Predictors:</u>

Table 8: Univariate analysis –Demographic risk factors for the development of severe envenomation following snake bite.

Variables	**Mild envenomation (N=32) n(%)**	**Severe envenomation (N=40)n(%)**	**Odds Ratio**	**95 % Confidence Interval**	**P-value**
Sex					
Male gender(n=53)	30 (75)	23(71.8)			
Female gender (n=19)	10 (25)	9(28.2)	0.85	0.29 – 2.43	0.765
Address					
Tamilnadu(n=51)	*24 (60)*	*27(84.4)*			
AndhraPradesh(n=21)	*16 (40)*	*5(15.7)*	*3.6*	*1.14 – 11.3*	***0.028****
Snake Identified	17 (42.5)	13(40.7)	0.92	0.36 – 2.37	0.873
Snake brought with patient	4 (10)	7(21.9)	2.52	0.66 – 9.53	0.173
First Aid	26 (65)	23 (71.9)	1.37	0.50 – 3.77	0.535
Tourniquet	25 (62.5)	19 (59.4)	0.87	0.34 – 2.27	0.787
Local Herbs	7 (17.5)	5 (15.6)	0.87	0.24 – 3.06	0.832
Native treatment use	2 (5)	4 (12.5)	2.71	0.46 – 15.87	0.268

On analysis of various demographic characteristics associated with patients presenting with snake bite, the predictors were "region of residence", with patients presenting from Tamil Nadu having a significant chance of developing severe envenomation with an Odds ratio of 3.6 (p value = 0.028) than patients presenting from Andhra Pradesh. Factors such as sex, identification of the snake, first aid, usage of tourniquet and native medication were not significantly associated with severe envenomation.

Clinical Predictors:

Table 9: Univariate analysis – Clinical risk factors for the development of severe envenomation following snake bite.

Variables	Mild envenomation (N=32)n(%)	Severe envenomation (N=40) n(%)	Odds Ratio	95 % Confidence Interval	P-value
Fang Mark	33 (82.5)	23 (71.9)	0.54	0.17 – 1.66	0.285
Prior ASV	30 (75)	26 (81.25)	1.44	0.46 – 4.51	0.527
ASV Hypersensitivity	12 (30)	4 (12.5)	0.33	0.09 – 1.15	0.084
Local Swelling	32 (80)	31 (96.9)	7.75	0.91 – 65.65	0.060
Local Pain	34 (85)	31 (96.9%)	5.47	0.62 – 48.02	0.125
Cellulitis	*24 (60)*	*29 (90.63)*	*6.44*	*1.67 – 24.77*	***0.007****
Necrotising Fasciitis	4 (10)	6 (18.75)	2.07	0.53 – 8.10	0.293
Local Bleeding	*20 (50)*	*26 (81.25)*	*4.3*	*1.46 – 12.79*	***0.008****
Systemic Bleed	*8 (20)*	*17 (53.13)*	*4.53*	*1.6 – 12.53*	***0.004****

Haematuria	5 (12.5)	9 (28.13)	2.73	0.81 – 9.21	0.104
Epistaxis	1 (2.5)	2 (6.25)	2.62	0.22 – 30.04	0.444
Gum Bleed	1 (2.5)	5 (15.63)	7.22	0.79 – 65.33	0.078
Compartment syndrome	1 (2.5)	5 (15.63)	4.42	0.49 – 40	0.216
Neurotoxicity	*22 (55)*	*26 (81.25)*	*3.54*	*1.19 -10.48*	***0.022****
Ptosis	19 (47.5)	20 (62.5)	1.84	0.71 – 4.75	0.206
Diplopia	13 (32.5)	17 (53.13)	2.35	0.90 – 6.14	0.080
Tachypnoea	25 (62.5)	25 (78.13)	2.14	0.74 – 6.15	0.157
Paradoxical respiration	5 (12.5)	8 (25)	2.33	0.68 – 8.00	0.178
Ventilation	*2 (5)*	*11 (34.38)*	*9.95*	*2.01 – 49.20*	***0.005****
Renal Failure	*11 (27.5)*	*26 (81.25)*	*11.42*	*3.70- 35.25*	***<0.001****
Requiring blood transfusion	*2 (5)*	*10 (31.25)*	*8.63*	*1.73 – 43.05*	***0.009****
Antibiotic Usage	32 (80)	31 (96.9)	7.75	0.91 – 65.65	0.060

On analysis of various clinical characteristics associated with patients presenting with snake bite, the clinical predictors of severe envenomation were presence of cellulitis at admission (90.63% vs 60%, p value= 0.007), presence of local bleeding (81.25% vs 50%, p value=0.008), presence of systemic bleeding (53.13% vs 20%, 0.004), features of neurotoxicity at admission (81.25% vs 55%, p value=0.022), requirement of ventilation during the ward stay (34.38% vs 5%, p value=0.005), presence of renal failure (81.25% vs 27.5%, p value= <0.0001), requirement of blood or blood product transfusion during the course of the hospital stay (31.25% vs 5%, p value= 0.009).

Laboratory parameters:

Table 10: Univariate analysis – Laboratory risk factors for the development of severe envenomation following snake bite.

Variables	Mild envenomation N=32 n(%)	Severe envenomation N=40 n(%)	Odds Ratio	95 % Confidence Interval	P-value
Anaemia	*4 (10)*	*14 (43.75)*	*6.99*	*2.01 – 24.35*	***0.002***
Leucocytosis	24 (61.54)	25 (78.13)	2.23	0.77 – 6.42	0.137
Thrombocytopenia	*7 (17.95)*	*19 (59.38)*	*6.68*	*2.26 – 19.67*	***0.001***
Icterus	*4 (10.53)*	*16 (50)*	*8.5*	*2.44 – 29.56*	***0.001***
Hepatitis	*2 (7.69)*	*10 (50)*	*12*	*2.21 – 64.89*	***0.004***
Rhabdomyolysis	21 (70)	26 (89.66)	3.71	0.89 – 15.4	0.072
Hematuria on urinalysis	*16 (40)*	*26 (81.25)*	*6.5*	*2.18 – 19.33*	***0.001***
Low fibrinogen	1 (33.3)	4 (28.57)	0.80	0.05 – 11.5	0.870
Prolonged WBCT	22 (56.41)	14 (43.75)	1.66	0.64 – 4.27	0.409
Prolonged Prothrombin Time	21 (52.50)	11 (34.38)	2.11	0.80 – 5.49	0.155
Prolonged APTT	36 (90)	23 (71.88)	2.54	0.69 – 9.37	0.215
Prolonged TEG/ROTEM	*2 (8)*	*16 (72.73)*	*30.66*	*5.5 – 171.7*	***<0.0001***

On analysis of various laboratory characteristics associated with patients presenting with snake bite, the predictors of severe envenomation were presence of anaemia (43.75% vs 10%, p value=0.002), thrombocytopenia (59.38% vs 17.95%, p value=0.001), jaundice (50% vs 10.53%, p value=0.001), hepatitis (50% vs 7.69%, p value = 0.004), haematuria on urinalysis (81.25% vs 40%, p value=0.001), prolonged Thromboelastography (72.73% vs 8%, p value= <0.0001). Other factors such as

leucocytosis, rhabdomyolysis, prolongation of whole blood clotting time, prothrombin time, activated partial Thromboplastin time were not significantly associated with severe envenomation.

Multivariate analysis:

Multivariate (adjusted) analysis using logistic regression methods was done for the fourteen variables (i.e. address, cellulitis, local bleeding, systemic bleeding, neurotoxicity, ventilation, renal failure, blood transfusion, anaemia, thrombocytopenia, jaundice, hepatitis, haematuria on urinalysis, prolonged Thromboelastography) were shown to be significant predictors of envenomation on univariate (unadjusted) analysis. None of the factors were found to be significant predictors of severe envenomation on multivariate analysis statistically.

Comparison of conventional coagulation tests with thromboelastography:

A) With respect to severity of snake envenomation:

Table 11: 2 x 2 contingency table showing the results of various tests of coagulation relative to severity of snake envenomation according to the snake bite severity score after snake bite.

Test of Coagulation	Number of patients with severe envenomation (severity score >= 8) (N=25)	No of patients with mild/ moderate envenomation (severity score < 8)(N=22)	Total number of patients (N=47)
20 Minute WBCT			
Prolonged	14	8	22
Normal	11	14	25
Prothrombin Time			
Prolonged	16	7	23
Normal	9	15	24
APTT			
Prolonged	7	2	9
Normal	18	20	38
TEG/ROTEM			
Prolonged	23	6	29
Normal	2	16	18

WBCT: Whole Blood Clotting Time, APTT: Activated Partial Thromboplastin Time, TEG: Thromboelastography, ROTEM: Rotational Thromboelastometry

Further statistical analysis was performed using the chi-square test with Yates correction where appropriate and the results are as follows:

Table 12: Table showing sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ration and odds ratio of various coagulation tests based on an abnormal test result being associated with severe envenomation after a snake bite.

Tests of Coagulation	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR	OR
20 Minute WBCT	56	63.6	63.6	56	1.54	0.69	2.23
Prothrombin Time	64	68.2	69.6	62.5	2.01	0.53	3.81
APTT	28	90.9	77.8	52.6	3.08	0.792	3.89
TEG/ROTEM	92	72.7	79.3	88.9	3.37	0.11	30.7

PPV: Positive Predictive Value, NPV: Negative Predictive Value, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, OR: Odds Ratio.

When used to predict a clinical course of severe envenomation, TEG/ROTEM had a sensitivity of 92% and specificity of 72.7%. The predictive value of an abnormal (prolonged) TEG/ROTEM for a severe clinical course was only 79.3% whereas the negative predictive value i.e. the predictive value for a mild course when TEG/ROTEM was normal was 88.9%. Whole blood clotting time, prothrombin time and activated partial Thromboplastin time had a sensitivity of 56%, 64%, 28% and a specificity of 63.6%, 68.2%, 90.9% respectively.

B) With respect to Clinical finding of features of coagulopathy:

Table 13: 2 x 2 contingency table showing the results of various tests of coagulation relative to Clinical finding of features of coagulopathy after snake bite.

Test of Coagulation	Coagulopathy present clinically (N=32)	Coagulopathy absent clinically (N=15)	Total number of patients (N =47)
20 Minute WBCT			
Prolonged	19	3	22
Normal	13	12	25
Prothrombin Time			
Prolonged	21	2	23
Normal	11	13	24
APTT			
Prolonged	7	2	9
Normal	25	13	39
TEG/ROTEM			
Prolonged	26	3	29
Normal	6	12	18

WBCT: Whole Blood Clotting Time, APTT: Activated Partial Thromboplastin Time, TEG: Thromboelastography, ROTEM: Rotational Thromboelastometry

Further statistical analysis was performed using the chi-square test with Yates correction where appropriate and the results are as follows:

Table 14: Table showing sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ration and odds ratio of various coagulation tests based on an abnormal test result being associated with clinical manifestation of coagulopathy after a snake bite.

Tests of Coagulation	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR	OR
20 Minute WBCT	59.4	80	86.4	48	2.97	0.508	5.85
Prothrombin Time	65.6	86.7	91.3	54.2	4.92	0.397	12.4
APTT	21.9	86.7	77.8	34.2	1.64	0.901	1.82
TEG/ROTEM	81.3	80	89.7	66.7	4.06	0.234	17.3

PPV: Positive Predictive Value, NPV: Negative Predictive Value, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, OR: Odds Ratio.

When the tests of coagulation were compared with each other against clinically evident features of coagulopathy (either local or systemic bleeding), TEG/ROTEM had a sensitivity of 81.3% and specificity of 80%. The predictive value of an abnormal (prolonged) TEG/ROTEM was only 89.7% whereas the negative predictive value was only 66.7%. Other tests of coagulation such as 20 minute whole blood clotting time, prothrombin time and activated partial Thromboplastin time had a sensitivity of 59.4%, 65.6%, 21.9% and a specificity of 80%, 86.7%, 86.7% respectively.

Correlation of Thromboelastography with thrombocytopenia:

Table 15: 2 x 2 contingency table showing the results of TEG tracing suggestive of thrombocytopenia with laboratory finding of thrombocytopenia after snake bite

(TEG tracing suggestive of platelet dysfunction is: r value normal, k value high, angle and MA are decreased)

	Thrombocytopenia present	Thrombocytopenia absent
TEG tracing suggestive of thrombocytopenia	18	11
TEG tracing not suggestive of thrombocytopenia	1	17

Sensitivity: 94.74%

Specificity: 60.71%

Positive likelihood ratio: 2.41

Negative likelihood ratio: 0.09

Positive predictive value: 62.07%

Negative predictive value 94.44%

Odds Ratio: 27.81

Confidence interval: (3.23-239.24)

p value: 0.0001

When the TEG tracings suggestive of thrombocytopenia were compared to actual laboratory evidence of thrombocytopenia the sensitivity of the test picking up a low platelet count was 94.74% and the negative predictive value i.e. a normal TEG ruling out a low platelet count was 94.44% (p value = 0.0001).

DISCUSSION:

Demographic, Clinical and Laboratory Characteristics:

Age and Sex:

The mean age of the study population was 40.78 years with a standard deviation of ±13.5 years. A significant proportion of the study population were males (53, 74%). The male to female ratio was 2.78:1. Snake bites were more common among males and a similar trend was present in all the age groups of <20, 21 – 40, 41 – 60, >60 years of age. The maximum number of males with snake envenomation belonged to the age group of 41 – 60(n=23) closely followed by age group of 21 – 40(n=22). Equal numbers of females with snake envenomation were present in the age groups of 21 – 40 and 41 – 60 years which also had the highest number of bites. There was only one case below the age of 20 and no patients in this category above the age of 60 years.

Similar observations were made in studies conducted by Kulkarni et al in Karnataka in 1994(8) and Ganneru B and Sasidhar RB in 2007 in Andhra Pradesh.(12)However one study conducted in Manipal by Montenerio et al found a female predominance with male to female ratio of 1:1.5.(83)

The predominant age group being affected between 20-40 years was consistent with all the earlier studies conducted in India, however two studies by Hansdak et al (34.5%) in Nepal(84) and Rahman et al(85) in Bangladesh (46%) which could be due to problem of child labour or children being taken to the field.

Occupation: In the present study majority of the patients were daily wage labourers working in the fields (34%), followed by farmers (29%). This was

consistent with the rural predominance and field related occupations like farmers and daily wage labourers being the most common group affected in various studies conducted for example Hansdak SG(84), Brunda and Sashidhar(12) and Bawaskar et al.(13)

Time of occurrence: In our study we found that most of the snake bites 32% occurred during the morning period (6am to 12 am) and 30% occurred during the evening period (6pm to 12 pm). This was different to the findings in other studies conducted in Maharashtra by Bawaskar HS et al (2008)(13) and in Manipal by Monterio NP et al (2010).(83)

Presence of fang mark and Site of Bite: In our study fang mark was identified in 78% of the patients. Both the lower combined constituted about 80% of the bite sites with rest occurring over the upper limb. We had one patient with a bite over the anterior abdominal wall leading to extensive necrosis and death later. Our lower limb predominance is consistent with studies conducted by Kulkarni ML et al in Karnataka(8) and Bawaskar HS et al in rural Maharashtra(13).

First Aid: Our study showed that 68% of the patients received some form of first aid prior to presentation to the hospital. Almost all of them received more than one form of first aid. Around 81% of the patients were administered this first aid by untrained personnel (either patient himself or the bystander). The predominant mode of first aid that was used was application of pressure tourniquet which was used by 71% of the patients that received first aid. 19% of the population had received a local anaesthetic injection at the bite site by the local practitioner to relieve the pain. Around 10% of the patients had treatment with native medicine in the form of local application of crushed herbs or special powder.

Older methods of first aid that were reported in earlier studies such as application od stones at the bite site, multiple incision, manual squeezing of the venom were not reported by any patients in the study. This shows a probable increase in awareness among the general population about snake envenomation. However giving a local anaesthetic injection by the primary health care doctors at the local site which is not recommended by any guideline shows the poor level of training even among the doctors or paramedics working at the rural level.

Type of Snake: Our study showed that around 42% of the patients were able to identify the snake and Russell's viper was the most common cause in them (31%) which was similar to studies conducted by Kulkarni et al -38%(8) and Kalantri et al - 24%.(86) However studies done by Bawaskar et al in Maharashtra and showed krait being the most common, Sharma SK et al showed cobra being the most common suggestive of the regional difference in the distribution of snakes in India.

Clinical manifestations:

Local Signs: Of the 72 patients that were studied, fang marks were present in 56 patients (78%). Local swelling was present in 87.50% of the patients. Features of cellulitis (such as local warmth with along with redness, swelling and tenderness) were present in 73.6% of the population. 64% of the patients had some amount of local bleed/ooze at the bite site. 14% went on develop necrotising fasciitis and 8.3% of the patients had compartment syndrome which required fasciotomy. The findings in our study were consistent with studies done by in Maharashtra by Bawaskar HS et al (2008)(13) and in Manipal by Monterio NP et al (2010).(83)

Systemic Features:

The various syndromes of snake envenomation seen in our study were:

1. Local Swelling only -10%
2. Hemotoxicity with/without Local swelling – 18%
3. Neurotoxicity only – 4%
4. Neurotoxicity with local swelling – 8%
5. Hemotoxicity + Neurotoxicity + Local swelling -18%
6. Hemotoxicity + Neurotoxicity + Renal failure + Local swelling – 42%

Hemotoxic features were noted in 35% of the patients with gross haematuria being the most common type seen in 40% and hematemesis seen in 20% of the patients. 1 patient has intra-abdominal bleed and 2 patients had intracranial bleeds resulting fatal outcome.

Neurotoxic features were present in 67% of the patients with ophthalmic symptoms such as ptosis and diplopia together constituting about 84% of the manifestations.

Renal failure was seen in 51.4% of the patient population with 19.5% of them requiring one or more episodes of dialysis.

This was consistent with the studies conducted earlier by Kulkarni et al(8), Bawaskar et al(13) Hansdak et al(84) and Sharma et al (87).

The syndrome of combined hemotoxicity, neurotoxicity, renal failure with local envenomation was highest which was in correlation with the high incidence of viper bite that were observed in the study sample.

Anti-Snake Venom: We found that 78% of the patients had received ASV prior to coming to our hospital. The remaining 22% of the patients were ASV naïve and received later in our hospital.

The mean ASV received was 17.6 ± 7.7 vials on the whole. Among this the mean ASV received outside was 6.3 vials and the mean ASV received in the hospital was 11.25 ± 6 vials.

Hypersensitivity to Anti-snake venom was noted in 22% (16 patients). Among this the incidence of mild hypersensitivity was 75% (overall 16.5%) and incidence of severe hypersensitivity reaction was 25% (overall 5.5%). The incidence of hypersensitivity was much higher compared to other studies like Kulkarni et al (1.2%)(8) and Sharma N et al (14%)(87). This could be explained by referral bias in view of the fact that many patients could have been referred to our hospital in view of developing hypersensitivity elsewhere, hence the high incidence.

Mortality: The mortality in our study was only 4.1% which was also seen in study done by Hansdak SG et al in Nepal(3.8%)(84) and Kulkarni et al (5.4)% (8) However much higher rates of mortality have been reported in study by Kalantri et al (11%)(86).

Risk factors for the development of severe snake envenomation:

The risk factors for the prediction of severe envenomation were divided into demographic, clinical and laboratory groups.

Demographic factors: The demographic risk factor associated with development of severe envenomation was that if the patient was a resident from Tamil

Nadu. (OR=3.6, p=0.02) The possible explanation for this could be that as this was a referral centre more sick patients had come from the home state of Tamilnadu and only few people would have been referred from the neighbouring state. Most of the sick patients from Andhra Pradesh would have been referred to a higher centre in that state itself. However this factor was not found to have independent significance on multivariate analysis.

Other risk factors that were associated with higher risk but did not have any statistical significance were not receiving first aid (OR=1.37, p = 0.137), usage of native treatment such as powders and herbs (OR=2.71, p =0.268), snake brought with the patient. (OR=2.52, p = 0.173). This would have probably delayed admission to hospital hence delayed ASV, thereby causing a severe clinical syndrome.

Clinical factors: On analysis of various clinical characteristics associated with patients presenting with snake bite, the clinical predictors of severe envenomation were presence of cellulitis at admission (OR= 6.44, p value= 0.007), presence of local bleeding (OR=4.3, p value=0.008), presence of systemic bleeding (OR=4.53, 0.004), features of neurotoxicity at admission (OR=3.54, p value=0.022), requirement of ventilation during the ward stay (OR=9.95, p value=0.005), presence of renal failure (OR=8.63, p value= <0.0001), requirement of blood or blood product transfusion during the course of the hospital stay (OR=8.63, p value= 0.009). Again on unadjusted multivariate analysis none of these factors were found have independent statistical significance.

Clinical features associated with higher risk but not statistically significant were administration of ASV at a local centre (OR=1.44, p value=0.527), local swelling (OR=7.75, p=0.06), local pain (OR=5.47, p value=0.125), necrotising

fasciitis (OR=2.07, p value=0.293). Though local and systemic bleeding were significant predictors, factors such as specific type of bleed like epistaxis (OR=2.62, p=0.44), gum bleed (OR=0.078), haematuria (OR=7.22, p= 0.07) were not statistically significant. Similarly specific manifestations of neurotoxicity like ptosis (OR=1.84, p=0.20), diplopia (OR=2.35, p =0.08) and paradoxical respiration (OR=2.33, p =0.178) were not statistically significant in spite of having higher odds ratio on analysis.

Laboratory factors: On analysis of various laboratory characteristics associated with patients presenting with snake bite, the factors associated with statistical significance on univariate analysis were presence of anaemia (OR=6.99, p value=0.002), thrombocytopenia (OR=6.68, p value=0.001), jaundice (OR=8.5, p value=0.001), hepatitis (OR=12, p value = 0.004), haematuria on urinalysis (OR=6.5, p value=0.001), prolonged Thromboelastography (OR=30.66, p value= <0.0001). None of the factors were found to have statistical significance on multivariate analysis.

Other factors such as leucocytosis (OR=2.23, p =0.137), rhabdomyolysis (OR=3.71, p=0.07), prolongation of whole blood clotting time (OR=1.66, p= 0.40), prothrombin time (OR= 2.11, p= 0.155), activated partial thromboplastin time (OR=2.54, p=0.215) though had higher odds ratio they were not statistically significant as shown by their p values.

Regional relevance - Comparison with Indian Data:

A study in department of Medicine in Kottayam Medical College, Kerala found that capillary leak syndrome, intracerebral bleed and respiratory paralysis as risk factors for mortality. Leucocytosis (OR=3.7), severe coagulopathy (OR=8) and late administration of ASV was associated with higher risk of complications. However none of these factors were significant on unadjusted analysis.(14)

A study conducted by Department of Medicine in the government hospital in Nagpur studied 262 patients with snake envenomation. The significant predictors of mortality on multivariate analysis were bleeding tendency (p= 0.013), mean PTTK (p= 0.047), respiratory failure (p= 0.045), shock (p= 0.013), mean ASV dose ($p < 0.001$).(88)

A study conducted by Mahatma Gandhi institute of Medical Sciences, Wardha collected patient data over a three year period. Of the 277 patients analysed, 11% was the mortality rate. Vomiting [OR 6.51 , $P \leq 0.002$], neurotoxicity [OR 3.15,$P = 0.004$] and admission serum creatinine concentration [OR 1.35, $P \leq 0.001$] were associated with higher risk of death in the adjusted analysis.(89)

On comparing our study with the afore-mentioned studies the following points were evident:

1) There have been very few prospective studies conducted on this topic. Most of the studies were retrospective studies with chart analysis. This may have led to observer bias and the data documentation is always not very reliable.
2) Most of the studies have compared the risk factors in relation to mortality. The mortality rates in the studies have a wide range from 3%(14) to 20%.(84)

3) Like our study though multiple factors were found to be significant on adjusted univariate analysis, on the unadjusted multivariate analysis no particular risk factor was found to be significant for prediction of a severe clinical course or envenomation.

Role of Thromboelastography (TEG/ROTEM) in snake envenomation:

The physician attending a patient who had a snake bite is usually in a very undecided state and needs to be very vigilant for development of further complications. Very close and intensive monitoring is required. Multiple studies have already proved that detection of coagulopathy could be a very useful and specific indicator that envenomation has happened.(54,55,62,64,65) Therefore a very sensitive test such as TEG which assesses the dynamic coagulation status has a potentially useful role in this situation.

Our study showed TEG having a sensitivity of 92% as compared to a sensitivity of 64% for prothrombin time and 56% for whole blood clotting time in predicting a higher disease severity. Also TEG had a negative predictive value of 88.9% compared to 56% for WBCT and 62.5% for prothrombin time, suggesting that a normal thromboelastogram can safely predict that severe envenomation may not have occurred and the patient is going to have a milder clinical course. However, all the three tests in comparison were not very good predictors (WBCT-63.6%, PT-69.6%, TEG-79.3%) of severe outcome (low specificity) in case of an abnormal test. The **study done by Hadley et al also have similar outcomes** with negative predictive value and sensitivity of TEG being 94%.(81) However the specificity for TEG was much lower in their study (45.5%) when compared to our results (72.7%).On searching PUBMED and INDMED

we could not find any earlier studies done on the role of Thromboelastography on snake bite done in India.

On comparison of the coagulation tests to detect coagulopathy when patients had clinical evidence of bleeding present TEG had a higher level of sensitivity (81.3%) as compared to WBCT (59.4%) and prothrombin time (65.6%). TEG had a slightly better negative predictive value of 66.7% compared to WBCT(48%) and prothrombin time(54.2%). However the specificity of all three tests were almost similar (80% for TEG and WBCT, 86.7% for prothrombin time.

It is well known that TEG can not only provide information regarding coagulation but also information regarding the components required such as platelets. When the TEG tracings suggestive of thrombocytopenia were compared to actual laboratory evidence of thrombocytopenia the sensitivity of the test picking up a low platelet count was 94.74% and the negative predictive value i.e. a normal TEG ruling out a low platelet count was 94.44% (p value = 0.0001).

Hence we conclude that though Thromboelastography cannot replace the importance of clinical assessment in patients with snake envenomation or the need for continuous monitoring and reassessment, it can serve as an early warning signal in few patients where it is abnormal. As the predictive value of a prolonged TEG/ROTEM for a severe clinical course is high such patients may need more careful observation and more aggressive treatment. Similarly a normal TEG can reasonably assure that envenomation is not severe and the clinical course of the patient is going to be benign. The role of Thromboelastography needs to be further studied in areas of need such as snake bite and further assessment in comparison to the amount of ASV given and treatment outcome with a study involving a larger sample size.

CONFOUNDERS:

Several studies have shown that conditions such as haematological or solid organ malignancies, chronic liver disease, anticoagulant or antiplatelet medications, immediate post-surgical period can interfere with the coagulation process and cause differences in the laboratory tests of haemostasis including TEG. Hence patients with these factors were excluded at enrolment itself to prevent the confounding factor bias.

Other factor which could have influenced the outcome of TEG results is the probable effect of reperfusion injury on coagulation caused by the use of a tight tourniquet after it is released. The usage of tourniquet was in 40 out of the 47 (85%) patients that were assessed for comparison of TEG with other parameters. As most of the patients used tourniquet, it was unlikely that this reperfusion injury could have affected the results.

LIMITATIONS:

1. The recruitment of patients in the study was planned as a consecutive sampling. Due to practical constraints, there were small lapses, despite which, consecutive sampling was attempted to the best possible extent.
2. The study protocol included coagulation testing at admission and 6 hours. However, repeat coagulation testing at more regular intervals, may have been ideal till the time of discharge; due to practical and financial feasibility constraints, this could not be done.
3. This study was restricted to the patients presenting to CMC. There were other specialties like paediatrics and other CMC branches like CMC Community centre, Bagayam and Government Vellore Medical College locally, which also admitted patients with snake bite. They had not been considered for inclusion into the study

as per protocol. So CMC being a referral hospital would have led to us seeing the more morbid patients; hence a bias towards patients with higher severity of envenomation. The prevalence of risk factors may have been higher in those patients from the aforementioned areas. Exclusion of these patients creates a lacuna in our understanding of this problem.

4. The number of patients with mild envenomation was considerably less than those with severe snake envenomation when coagulation tests were evaluated. As missing data for TEG was present in few patients, these patients had to be excluded from the final statistical analysis. Therefore, finally even though 47 (72 totally) patients were enrolled into the study within the given time frame, the numbers within each category was not adequate to elucidate associations by statistical analysis. Hence the results of the primary objective of the study, aiming to look at the ability of TEG to detect the coagulation abnormalities in snake envenomation could not be accurately interpreted or extrapolated.
5. Although the usual laboratory parameters like haemoglobin platelets were available for all patients, expensive tests such as fibrinogen could not be done as this was not included in the study protocol. Other tests results such as APTT waveform analysis, levels of fibrin degradation products, fibrinogen and thrombin antithrombin complex levels, level of snake venom in the plasma, ELISA to detect the snake type would have been helpful in analysing and better understanding of the coagulopathy process.
6. There were only 4 patients admitted with pure neurotoxic envenomation and the results of coagulation testing were equivocal in them. Larger sample size of pure neurotoxic snake bites would be necessary to delineate the role of TEG in assessing envenomation in that subgroup.

7. Most of the patients had received ASV already prior to admission. This is an inherent problem in being a tertiary referral care centre and hence the results of coagulation testing could have been affected.
8. Though TEG tracings showed good correlation with thrombocytopenia, TEG cannot accurately distinguish between platelet dysfunction or decrease in platelets. Platelet dysfunction studies were out of scope of this study as they are expensive. Hence this point needs to be kept in mind while interpreting the results of this study.

MERITS

Our study is one of the few prospective studies in the country to describe snake envenomation as most of the studies have been retrospective analysis by case records. It is the first study in India, to describe the role of Thromboelastography testing in the setting of snake bite envenomation. It is also the first in India to compare Thromboelastography with other coagulation testing in snake bite. The need for identification of a better and comprehensive test of assessment for a very common and significant problem of snake bite in the community in the absence of specific diagnostic kits was the driving force behind this study.

A uniform protocol for management of snake bite is followed by all the doctors in the medical units and emergency department, as a result of which all the patients studied were on standard treatment. Therefore, the treatment bias of anti-snake venom affecting a particular coagulation test was reduced. Hence the results of all the coagulation tests would have been similarly affected.

CONCLUSIONS

1. Thromboelastography is a more sensitive test of coagulopathy in snake envenomation than the tests used conventionally such as WBCT and prothrombin time. (92% vs 56%, 64%).
2. Thromboelastography is a more sensitive test of identifying severe cases of snake envenomation than the tests used conventionally such as WBCT and prothrombin time. (81.3% vs 59.4%, 65.6%).
3. A normal thromboelastogram has a better predictive value of a milder clinical course than a normal Whole blood clotting time or Prothrombin time (NPV=88.9%).
4. Thromboelastography can significantly predict thrombocytopenia in cases of snake envenomation (OR=27.81, p value = 0.0001)
5. Though we found multiple risk factors significant on univariate analysis to predict a severe clinical course, none of the variables were statistically significant on multivariate analysis.
6. Socio-demographic variables, clinical findings, laboratory and treatment variables, ASV related data and mortality in our study were found to be consistent with studies done earlier.

Snake envenomation can be considered as one of the most neglected health problem in the country where prompt and appropriate therapy with adequate support can make a significant difference. Unfortunately not much research has gone into such an important public health problem and most of the studies conducted have been largely retrospective descriptive studies. Studies have shown that despite advancement of medical care in the rural areas and availability of ASV the mortality

related to snake envenomation has largely remained same. The main tests used for diagnosis and monitoring therapy still remain the traditional tests for coagulation namely WBCT and prothrombin time. Our study shows that Thromboelastography is a better sensitive test for identification of coagulation abnormalities and for prediction of severe envenomation than the routine tests of clotting. Our study also shows that a normal thromboelastogram has a higher prediction of a milder clinical course. Hence in areas of the world such as India where specific venom detection kits to detect envenomation are not available, newer tests such as TEG would provide a reasonable alternative to identify envenomation.

Hence from this study we recommend that:

1. Thromboelastography can be a useful adjunct to management of snake envenomation and in places where the testing is available it may be worthwhile consider doing it to make a better clinical decisions.
2. Further studies comparing Thromboelastography must be done in patients with snake bite with larger sample size to prove the better sensitivity and specificity of TEG compared to conventional tests.
3. Further studies are required to assess the role of TEG if it can play a role in determining the amount of ASV to be given or its use in determining the Transfusion requirements (platelet and FFPs) in patients with acquired DIC as a result of snake envenomation.

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APPENDICES

APPENDIX 1: INFORMED CONSENT

INFORMED CONSENT FOR SNAKE ENVENOMATION STUDY

Christian Medical College, Vellore

Department of Medicine

Title: An observational trial comparing Thromboelastography with conventional coagulation assays to assess disease severity in patients with snake bite**.**

Information sheet

You are being requested to participate in a study to see if a test called thromboelastography can help us predicting disease severity better than routine tests in patients with snake bite. There are no side effects expected as this is an observational study. We hope to include about 100 people from this hospital in this study.

What is thromboelastogram?

Thromboelastogram is a blood test which is used to assess the clotting function of the blood.

What is the reason for the study? Are the tests currently being used good enough?

Traditionally snake envenomation is diagnosed and clotting ability of the blood is monitored by routine tests like whole blood clotting time and prothrombin time which also form the basis for administration of ASV to the patients. Therefore it is important to accurately know the coagulation status of the patients at admission for effective administration of ASV. Thromboelastography is a new test which also assesses the clotting profile. Hence we are comparing the older tests with a newer test. This may in future help us in better management of patients with snake bite.

Does thromboelastogram have any side effects?

No, thromboelastogram will not have any side effects. However, it has same chance of injury during the collection of blood sample for any other test.

If you take part what will you have to do?

If you agree to participate in this study, you will be asked to give two blood samples of 3 ml each at admission and after 6 hours along with the routine samples. All other treatments that you are already on will be continued and your regular treatment will not be changed during this study. You will also be administered a questionnaire at the time of admission.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way

What will happen if you develop any study related injury?

We do not expect any injury to happen as this is a observational study. We are unable to provide any monetary compensation, however.

Will you have to pay for the study testing?

No, thromboelastography will be done at free of cost. Any other treatment that you usually take will continue but the usual arrangements that you have with the hospital will decide how much you pay for this.

What happens after the study is over?

You may or may not benefit from the study test that you have given. Once the study is over, we wish to analyze the results and see if this test is better than the earlier tests. This would help us in managing patients with snake bite better in the future.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask

Dr. HARSHA TEJA PERLA,

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DEPARTMENT OF MEDICINE

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CONSENT TO TAKE PART IN A CLINICAL TRIAL

Study Title:*An observational trial comparing Thromboelastography with conventinal coagulation assays to assess disease severity in patients with snake envenomation.*

Study Number:

Participant's name:

Date of Birth / Age (in years):

I_____

_____, son/daughter of _____

(Please tick boxes)

- Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]
- I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]
- I also understand that during the period of the study, the test will be provided free, but after this, if the same test is prescribed, I may have to pay for it [ ]
- I understand that I will receive free treatment for any study related injury or adverse event but I will not receive and other financial compensation [ ]
- I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]
- I understand that my identity will not be revealed in any information released to third parties or published [ ]
- I voluntarily agree to take part in this study [ ]

Name: Name:

Signature: Area for thumb impression:

Name of witness: Signature of the parent/guardian (if age < 18)

Relation to participant: Name:

Date:

APPENDIX 2: CLINICAL RESEARCH FORM (DATA ABSTRACTION FORM)

General information

S.No: Patient Name / Label:

Age: Sex: male /female

Contact number: Occupation:

Address:

Epidemiology:

- **Environmental setting**: field / house / if others mention where?
- **Season**: February - June / July –September / October –January
- **Time of the day**:
- **Type of snake**: identified / not identified

If identified name of the snake:

Common names

English name	Tamil name	Telugu name
Indian Cobra	Naagupambu	Nagupaamu
Russells viper	RethaaunaliKannadiviriyan	Katukarekulapaamu or rakthapinjara/ pinjari
Saw scaled viper	Surattaipambu,viriyanpamboo, surutaivireyan	Thrachupaamu
Krait	Kattuviriyan, Pudayan	Katlapaamu

- **Time of presentation** (how many hours after the bite):
- Duration of hospital stay:
- First aid measures prior to admission to the hospital
    - **If yes,** please specify: tourniquet/ multiple incisions /herbal or native medicines.
- Whether ASV was administered before presentation to CMC: yes/no
    - If yes, how many vials of ASV:
- **Bite to needle time :**(time since the bite to time of first vial of ASV)

Clinical features:

1. **Fang marks** Y/N **if Yes** site of the bite?

2. **Local features** : (please tick)

   Inflammatory swelling / bleeding / ecchymosis / blister formation/ local necrosis

3. **Compartment syndrome**: Y/N **if Yes** did the patient require fasciotomy/other treatment?

Systemic manifestations:

i. **Hemorrhagic manifestations :**(internal bleeding or haemorrhage from other than local site) including hematemesis, hematuria, epistaxis, bleeding per rectum and bleeding gums

Yes /no if yes kindly mention the complication?

ii. Neurological manifestations :

a) Ptosis Y/N

b) Breathing difficulty requiring ventilator support Y/N

c) Severe muscular paralysis Y/N

d) Cranial nerve palsy or aphasia Y/N

e) Other neurological manifestations

Management:

a) Total ASV vials given outside :

b) Total number of ASV vials given in the hospital :

c) Average total number of days requiring ventilation :

d) Hypersensitivity to ASV: yes/ no

e) If hypersensitivity present then (tick one)

   1. Mild reaction : (itching, tachycardia, palpitations, cough, nausea, vomiting)

   2. Severe reaction : (bronchospasm, hypotension, angioneurotic oedema)

f) Did the patient require haemodialysis: Y/N if Y how many sessions?

g) Did the patient require blood transfusions :

h) Final outcome of the patient : completely recovered/ death/ residual sequelae

i) If residual sequelae, present kindly mention the sequelae?

Co morbidities:

Diabetes	Yes / No	**Malignancy**	Yes / No
Hypertension	Yes / No	**Prior antiplatelet therapy**	Yes / No
CKD	Yes / No	**IHD/CAD**	Yes / No
CLD	Yes / No	**History of bleeding disorder**	Yes / No

Laboratory results:

	At admission	After 6 hours
20 min whole blood clotting time		
Prothrombin time with INR		
Activated partial thromboplastin time (aPTT)		
TEG/ROTEM Thromboelastography 1) CT(Clotting Time): (in sec) 2) CFT(Clot Formation Time) (in seconds) 3) Alpha Angle : 50 – 68 (degree), 4) MCF(Maximum Clot Firmness) : 55 – 66 (mm)		
Fibrinogen		
CPK (creatine phosphokinase)		
Serum creatinine / electrolytes / urea		
LDH (lactate dehydrogenase)		
Liver function tests		
Haemoglobin		
Total counts		
Platelets		
Urinalysis		
Special tests : ultrasound/Doppler/CT Scan		

Snake bite severity score:

Criterion	Points
Pulmonary system	
No symptoms/signs	0
Dyspnea, minimal chest tightness, mild or vague discomfort, or respirations of 20 to 25	1
Moderate respiratory distress (tachypnea, 26 to 40 breaths/minute; accessory muscle use)	2
Cyanosis, air hunger, extreme tachypnea, or respiratory insufficiency/failure	3
Cardiovascular system	
No symptoms/signs	0
Tachycardia (100 to 125 beats/minute), palpitations, generalized weakness, benign dysrhythmia, or hypertension	1
Tachycardia (126 to 175 beats/minute) or hypotension, with systolic blood pressure greater than 100 mm Hg	2
Extreme tachycardia (>175 beats/minute), hypotension with systolic blood pressure <100 mm Hg, malignant dysrhythmia, or cardiac arrest	3
Local wound	
No symptoms/signs	0
Pain, swelling, or ecchymosis within 5 to 7.5 cm of bite site	1
Pain, swelling, or ecchymosis involving less than half the extremity (7.5 to 50 cm from bite site)	2
Pain, swelling, or ecchymosis involving half to all of extremity (50 to 100 cm from bite site)	3
Pain, swelling, or ecchymosis extending beyond affected extremity (more than 100 cm from bite site)	4
Gastrointestinal system	
No symptoms/signs	0
Pain, tenesmus, or nausea	1
Vomiting or diarrhea	2
Repeated vomiting, diarrhea, hematemesis, or hematochezia	3
Hematologic symptoms	
No symptoms/signs	0
Coagulation parameters slightly abnormal: PT, <20 seconds; PTT, <50 seconds; platelets, 100,000 to 150,000/mL; or fibrinogen, 100 to 150 µg/mL	1
Coagulation parameters abnormal: PT, <20 to 50 seconds; PTT, <50 to 75 seconds; platelets, 50,000 to 100,000/mL; or fibrinogen, 50 to 100 µg/mL	2
Coagulation parameters abnormal: PT, <50 to 100 seconds; PTT, <75 to 100 seconds; platelets, 20,000 to 50,000/mL; or fibrinogen, <50 µg/mL	3
Coagulation parameters markedly abnormal, with serious bleeding or the threat of spontaneous bleeding: unmeasurable PT or PTT; platelets, <20,000/mL; or undetectable fibrinogen; severe abnormalities of other laboratory values also fall into this category	4
Central nervous system	
No symptoms/signs	0
Minimal apprehension, headache, weakness, dizziness, chills, or paresthesia	1
Moderate apprehension, headache, weakness, dizziness, chills, paresthesia, confusion, or fasciculation in area of bite site	2
Severe confusion, lethargy, seizures, coma, psychosis, or generalized fasciculation	3

PT, prothrombin time; **PTT**, partial thromboplastin time.
Points are assessed on the basis of manifestations caused by the venom itself (antivenom reactions not included). Ranges given are for adults; appropriate compensation should be made for age.

Total score at admission: _____ (Mild - moderate 0-7, severe 8-20)

APPENDIX 3: STANDARD OPERATING PROCEDURES

3a. Rotational Thromboelastometry(ROTEM):

1.1 PURPOSE:

To check the coagulation state of a blood sample.

1.2 PRINCIPLE:

The ROTEM technology is based on a fixed cylindrical cup and a permanently oscillating vertical axis. The axis is supported by a high precision ball bearing and oscillates to the left and to the right through an angle of 4.75º. The rotation of the axis is driven by a motor that is connected to the axis via an elastic spring. For the measurement, a disposable plastic pin with 6 mm diameter is placed firmly on the axis and the blood sample is filled into a disposable 8 mm diameter cup and is then uplifted onto the measurement channel. Hence, the plastic pin is immersed into the blood sample. The rotation is detected optically via a mirror plate at the upper end of the axis, a diode as light source and a light sensitive sensor (CCD Chip). If no clotting takes place, the movement is not obstructed. When a clot is formed and attaches itself between pin and cup surfaces, the movement is obstructed. The result is a balance between the spring tension and the tension of the clot. As the clot becomes firmer, the rotational amplitude of the axis is reduced.

1.3 PRIMARY SAMPLE:

Citrated whole blood (platelet rich plasma can also be used)

1.4 MATERIALS:

1. Citrated whole blood
2. Disposable cups and pins
3. Pipettes (100-1000µl, 5-40µl)
4. 0.2M calcium chloride
5. Diluted thromboplastin (1/2000)
6. Personnel Protective Equipment (PPE)

1.5 SAMPLE PREPARATION:

Blood Sample:

Blood is preferably drawn via a 21G needle directly into vacuette Greiner tube containing 3.2% sodium citrate with minimal stasis.

The temperature of the sample may influence the measurement results.

Measure the blood sample directly after sampling.

If this is not possible, preheat the blood sample for 5-10 min before measurement in the sample preheating station of the ROTEM delta.

1.6 REAGENT PREPARATION:

Preparation of Tissue factor:

Dilute 10µl of recombiplastin into 490µl of Imidazole buffer in tube 1.

Add 50 µl of the contents in tube 1 to 950 µl of Imidazole buffer in tube 2 and mix well.

Add 500µl of the contents in tube 2 to 500 µl of imidazole buffer in tube 3 and mix well.

This diluted recombiplastin is used for the processing of a sample on ROTEM.

1.7 PROCEDURE:

Switching on the ROTEM system:

Activate the ROTEM system with the main switch on the back of the device.
Push the blue on/off button on the right hand side of the instrument.
Log in to the system
Touch the screen if the screen saver is active.
Select user (admin)
Enter password (admin)
Measurement module screen will open

Measuring Cell Preparation:

Mounting Pins:

Take the cup with the pin in it from the storage box. Push the pin in the cup onto the axis chosen for measurement.

Note: The status line under the channel is grey by default. In case the axis has been moved heavily when attaching the pin, the channel becomes inactive and the status line turns blue during the time of initialization. **Never touch the pin (not even with gloves)**

Placing Cups:

Place the cup with its opening facing upwards into the appropriate preheated cup holder. **Leave the cup holders always in the temperature controlled area**.

Fixing Cups:

Push and fix the cup in the cup holder using the MC Rod. **The cup must fit tightly.**

Enter Patient Data:

Touch one of the four channels.
In the upper part of the screen entry fields for patient data {Patient ID, Patient name (first name, last name, and comment} are displayed.
Touch the respective entry field.
Enter patient data.

1.8 PROCEDURE:

Add 20µl of 0.2M $CaCl_2$ prewarmed cup.
Add 30µl of diluted recombiplastin to a separate plastic vial.
Mix 500µl of well mixed whole blood the tissue factor.
Add 320µl of the mixture to the $CaCl_2$ and mix well.
Place the cup holder onto the measuring position using the guiding rods.
The cup holder is kept in measuring position by magnets.
Press the "Start manual" icon the screen.

1.9 INTERPRETATION:

During measurement, the large TEMogram is shown at the left upper side of the screen. In the upper right part of the screen, the current measurement results of the test parameters are shown.

ROTEM Parameters:

Clotting Time (CT): It is the time from the beginning of the test by adding the clot activator until the time when amplitude of 2 mm is achieved.

Clot Formation Time (CFT): It is the time between 2 mm amplitude and 20 mm amplitude of the clotting signal.

Alpha Angle (α): It is defined as the angle between the middle axis and the tangent to the clotting curve through the 2 mm amplitude point. It describes the kinetics of clotting.

Maximum Clot Firmness (MCF): It is the measure for the firmness of the clot and therefore the clot quality. It is the maximum amplitude that is reached before the clot is dissolved by fibrinolysis and the clot firmness falls again.

Maximum Lysis (ML): It is the degree of fibrinolysis relative to maximum clot firmness achieved during the measurement.

1.10 Possible Interference:

Clotted sample.

1.11 Safety protocols:

Always use the necessary PPE for all procedures done in the laboratory. Consider every biological sample as potential bio hazard.

3b. Prothrombin Time (PT)

2.1 Purpose

To look for the overall efficiency of extrinsic pathway of coagulation and monitoring of oral anticoagulant therapy.

2.2 Principle

Clot based assay.

2.3 Performance specifications

Limits of detection - 5 to >120 Sec

2.4 Primary sample

Citrated blood.

2.5 Type of container

1. Light blue top vacutainer.
2. 1ml mini collect Greiner Vacutte (For pediatric purposes)

2.6 Reagents and Materials

1. Innovin: product needs to be reconstituted as per product insert/instruction sheet, and prewarmed to 37°C. This reagent already contains $CaCl_2$.
2. Patient plasma, control plasmas as required. (NB: test normal plus abnormal QC plasma whenever a fresh vial of recombiplastin is reconstituted).
3. Waterbath, 12 x 75 test tubes, stop watches, yellow tips, and 100 and 200ul automatic pipettes and light source.

2.7 Procedure

1. Add 0.1ml plasma into duplicate small glass tubes placed in a 37°C water bath, and leave 3 min to equilibrate to 37°C. Add 0.2ml prewarmed innovin, and simultaneously start stop watches.

2. Mix and tilt tubes to nearly horizontal position at one second intervals, otherwise maintaining in 37°C water bath.
3. Depress stop watch mechanism on first appearance of a clot. The time taken for the clot to form (i.e. between addition of Innovin and the appearance of the clot) is the 'prothrombin time' (PT).
4. Take the mean of the duplicate readings (providing that they don't differ by more than two seconds; otherwise repeat the procedure and check the reagent; replace if necessary).

2.8 QC protocol

1. A normal control (e.g. pooled normal plasma [PNP]) and an abnormal control plasma (eg Coag-path from Stago) should also be included with every batch of patient plasma tested, or every few hours if testing a large number of plasmas throughout the day.
2. Run normal control and abnormal control plasma for 10 days and calculate the mean and +/-2SD. The control values should fall within +/-2SD.

2.9 Possible interference

1. Improper centrifugation.
2. Plasmafrom badly haemolysed blood**.** Badly haemolysed blood may give an artifactual coagulation results that do not accurately represent the coagulation status of the patient under investigation. Haemolysed blood may suggest a traumatic blood collection and you may need to request a repeat sample collection.
3. Highly lipemic sample
4. Blood not tested within four hours of collection.

2.10 Alert values

All the abnormal values.

2.11 Result interpretation

1. The results are expressed as a mean of the duplicate reading in seconds, both mean of the patient time and mean of the normal control time; the results are always interpreted with INR (International Normalized Ratio).
2. Normal Range. 10 – 12Secs.
3. (Normal values varies depending on the Thromboplastin used the exact technique under visual or automated end point reading is used)
   INR= Prothrombin Time (PT) of test plasma (sec)/ Mean Normal Prothrombin Time (sec)
   ISI = International Sensitivity Index.
   INR= International normalized ratio.
4. Ideally, laboratory should establish its own Mean Normal Prothrombin Time (MNPT). Classically, for the MNPT: this is obtained by testing at least 20 normal plasmas in that laboratory's PT assay, and taking the mean PT. Selected instrument specific ISI values are usually provided for each batch of Innovin.

2.12 Safety protocols

1. Always use the necessary PPE for all procedures done in the laboratory.
2. Consider every biological sample as a potential bio hazard.

3. Ensure that all laboratory work benches are mopped with 70% ethanol before and after work.
4. In case of any needle stick injury, take a patient sample & hospital number, wash the wound with soap and water, inform the any department staff/ DSA and rush to the SSHS.

2.1 Potential sources of variation/environmental impact on procedure

All samples must be processed within four hours of collection.

3c. Activated Partial Thromboplastin Time (APTT)

3.1 Purpose

To rule out overall efficiency of intrinsic and common pathway of coagulation and monitoring of heparin therapy.

3.2 Principle

Clot based assay

3.3 Performance specifications

Limits of detection – 20 to >180 Sec

3.4 Primary sample

Citrated blood.

3.5 Type of container

1. Light blue top vacutainer.
2. 1ml mini collect Greiner Vacutte (For pediatric purposes)

3.6 Reagents and Materials

1. SynthAsil (IL)
2. CaCl2 0.025M pre-warmed to 37°C
3. Patient plasma and control plasma
4. 12 x 75 glass tubes and stopwatches.
5. Water bath
6. Automated Pipettes/glass pipettes and tips.

3.7 Procedure

1. Add 0.1ml of plasma and 0.1ml APTT reagent in a glass tube (12 x 75) and place it in a 37°Cwater bath.
2. Mix, and leave for 5 minutes to equilibrate to 37 deg C and to provide suitable activation of plasma with contact factor.
3. Add 0.1ml of warmed 0.025M cacl2, and simultaneously start stopwatch.
4. Mix and tilt tubes to nearly horizontal position at one-second intervals, otherwise maintaining in 37 deg C water bath.

5. Depress stopwatch mechanism on first appearance of a clot. The time taken for the clot to form (i.e., between addition of CaCl2 and the appearance of the clot) is the APTT.
6. Always do in duplicates.
7. Take the mean of the duplicate reading (provided that they don't differ by more than 2 seconds otherwise repeat procedure and check reagents.

3.8 QC protocol

1. A normal control (e.g. pooled normal plasma [PNP]) and an abnormal control plasma (e.g. Coag-path from Stago) should also be included with every batch of patient plasma tested, or every few hours if testing a large number of plasmas throughout the day.
2. Run normal control and abnormal control plasma for 10 days and calculate the mean and +/-2SD. The control values should fall within +/-2SD.

3.9 Possible interference

1. Improper centrifugation of patient sample
2. Badly haemolysed bloodmay give an artifactual coagulation results that do not accurately represent the coagulation status of the patient under investigation. Haemolysed blood may suggest a traumatic blood collection and you may need to request a repeat sample collection.
3. Blood not tested *within four hours* of collection.

3.10 Alert values

All the abnormal values.

3.11 Result interpretation

1. Report APTT results in seconds for example control 30 sec, patient 36 sec.
2. Each lab has to establish their own range.
3. As a rough guide the APTT of normal plasma should be 25 to 35 sec.
4. In our lab a difference of more than 6 sec between the control and patient is considered as abnormal and needs further evaluation.

3.12 Safety protocols

1. Always use the necessary PPE for all procedures done in the laboratory.
2. Consider every biological sample as a potential bio hazard.
3. Ensure that all laboratory work benches are mopped with 70% ethanol before and after work.
4. In case of any needle stick injury, take a patient sample & hospital number, wash the wound with soap and water, inform the any department staff/ DSA and rush to the SSHS.

3.13 Potential sources of variation/environmental impact on procedure

All samples must be processed within four hours of collection.

DATA TABLES

patient	Sex	Age	agecode	Occu	Adrs	TOB	TESB	Modtrans	Snideyn	Sntype	Snbring	EnvSet	Durhosp
1	1	43	3	1	2	3	3	4	1	1	2	1	3
2	1	50	3	2	1	3	2	3	2	5	2	1	4
3	1	60	3	1	1	4	2	4	2	5	2	2	4
4	1	37	2	1	2	1	2	2	1	4	2	1	7
5	1	25	2	2	1	3	1	4	2	5	2	1	2
6	1	45	3	4	1	1	1	2	2	5	2	1	2
7	2	23	2	3	1	3	1	5	2	5	2	1	12
8	1	65	4	1	1	4	1	2	1	1	2	1	7
9	1	56	3	2	1	3	3	4	2	5	2	1	7
10	2	53	3	3	1	1	1	4	1	1	2	1	5
11	1	38	2	1	1	1	1	5	1	1	2	1	16
12	1	43	3	1	2	3	1	4	1	1	2	1	3
13	2	56	3	3	1	1	3	5	2	5	2	1	6
14	2	53	3	2	1	1	2	4	2	5	2	1	3
15	1	59	3	2	1	1	3	2	2	5	2	1	1
16	1	18	1	6	1	4	1	2	2	5	2	2	1
17	2	41	3	2	1	3	1	3	1	1	1	1	12
18	1	39	2	2	1	4	2	3	1	1	1	1	11
19	1	81	4	1	1	4	1	3	1	2	1	2	6
20	2	31	2	2	1	2	1	4	2	5	2	1	5
21	1	36	2	2	1	3	3	5	2	5	2	1	10
22	1	46	3	4	2	3	1	5	2	5	2	1	14
23	2	31	2	3	1	4	1	2	1	4	1	1	3
24	1	18	1	6	1	3	3	5	2	5	2	1	5
25	1	41	3	2	1	4	2	3	2	5	2	2	6
26	1	56	3	2	2	1	1	3	1	1	2	1	2
27	1	46	3	3	1	1	2	3	1	1	2	1	7
28	1	36	2	2	1	2	1	5	1	1	1	1	11
29	1	45	3	2	1	1	3	3	2	5	2	1	1
30	1	51	3	1	1	2	1	3	2	5	2	2	13
31	2	24	2	3	2	3	1	3	2	5	2	1	13
32	2	18	1	6	1	1	2	3	2	5	2	1	8
33	1	42	3	1	1	4	2	5	2	5	2	2	5
34	1	35	2	1	2	1	2	3	2	5	2	1	3
35	1	35	2	2	1	1	1	3	1	1	1	1	6
36	1	22	2	1	1	4	3	5	1	1	2	1	10
37	2	31	2	3	1	1	1	4	1	1	2	1	8
38	2	55	3	3	2	1	1	3	1	3	2	1	13
39	1	55	3	2	2	3	1	5	2	5	2	1	5
40	1	16	1	6	1	2	1	1	2	5	2	1	6
41	1	50	3	1	1	2	1	3	1	1	2	1	7
42	1	47	3	2	1	2	4	5	1	1	1	1	4
43	1	37	2	1	1	2	1	5	1	1	1	1	1
44	1	22	2	6	1	4	3	5	1	4	1	2	4
45	1	36	2	2	1	2	1	1	1	1	2	1	4
46	2	41	3	3	1	1	3	5	2	5	2	1	3
47	1	23	2	2	2	2	3	4	1	1	2	1	6

48	1	39	2	1	1	1	3	4	1	1	2	1	9
49	1	23	2	1	2	3	1	5	2	5	2	1	1
50	1	48	3	1	1	3	1	5	2	5	2	1	5
51	2	31	2	3	1	4	1	4	2	5	2	2	5
52	2	32	2	3	1	4	1	5	2	5	2	1	6
53	2	62	4	3	2	4	1	1	2	5	2	2	2
54	1	34	2	4	2	4	1	2	2	5	2	2	2
55	1	62	4	1	2	1	1	5	1	1	2	1	5
56	1	42	3	1	1	4	3	3	2	5	2	1	4
57	2	47	3	3	1	3	3	4	2	5	2	1	3
58	1	24	2	6	1	2	3	5	1	1	1	1	10
59	1	24	2	6	2	3	1	4	2	5	2	2	5
60	1	62	4	1	1	4	2	3	2	5	2	1	6
61	1	33	2	2	1	1	1	1	1	4	2	1	4
62	2	37	2	3	1	1	1	3	2	5	2	2	9
63	1	51	3	2	2	4	1	4	1	1	2	2	4
64	2	37	2	3	2	3	1	3	2	5	2	1	8
65	1	45	3	1	1	3	1	3	1	3	2	1	6
66	1	35	2	2	2	3	1	2	2	5	2	1	5
67	1	55	3	1	2	3	3	4	2	5	2	1	24
68	1	31	2	2	1	3	3	5	2	5	2	1	19
69	2	50	3	3	2	1	2	2	2	5	2	2	4
70	1	45	3	2	1	3	1	1	1	2	1	1	5
71	1	55	3	2	1	1	1	2	2	5	2	1	3
72	1	21	2	6	2	1	4	5	2	5	2	1	21

FirstAid	tornquet	herbnati	locanaes	TT	PriorASV	ASVout	ASVin	ASVtot	ASVHS	tyasvhs	BTNtime
1	1	2	2	1	1	4	12	16	2		6
1	1	2	1	1	1	2	10	12	2		2
1	2	1	2	1	1	10	8	18	2		9
2	2	2	2	1	1	2	18	20	2		8
2	2	2	2	1	1	8	10	18	2		5
1	1	2	2	1	1	8	4	12	1	1	3
1	1	2	2	1	1	17	22	37	2		4
2	2	2	2	1	2	0	16	16	2		2
1	1	2	2	1	1	12	4	16	2		1
1	1	2	2	1	1	8	6	14	2		2
2	2	2	2	1	1	8	14	22	2		1
2	2	2	2	1	1	4	12	16	1	2	2
1	2	2	2	1	1	24	4	28	2		4
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1	1	1	2	1	1	2	12	14	2		3
1	1	2	2	1	2	0	18	18	2		1
2	2	2	2	1	2	0	16	16	2		2
1	1	2	2	1	1	18	4	22	2		5

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1	1	2	2	1	1	8	12	20	2		1
1	1	2	1	1	1	2	10	12	1	1	4
2	2	2	2	1	2	0	20	20	2		8
1	1	2	2	1	1	1	4	5	2		1
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1	1	2	2	1	1	8	24	32	2		7
1	1	2	2	1	1	8	10	18	1	1	2
1	1	1	1	1	1	10	10	20	2		6
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1	1	2	1	1	1	8	8	16	2		2
2	2	2	2	1	1	11	4	15	2		4
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2	2	2	2	1	1	6	6	12	2		3
1	1	2	2	1	1	4	6	10	1	1	2
1	1	1	2	1	1	4	10	14	1	1	1
1	1	2	2	1	1	8	6	14	2		0.25
1	1	2	2	1	2	0	15	15	2		2.5
2	2	2	2	1	2	0	6	6	2		2
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1	1	2	2	1	1	4	18	22	1	1	1
1	1	2	2	1	1	8	12	20	1	1	1
2	2	2	2	1	1	2	12	14	2		1
2	2	2	2	1	1	2	12	14	2		0.5
1	1	2	2	1	1	10	25	35	2		3
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1	1	2	2	1	1	4	13	17	2		1
2	2	2	2	1	2	0	10	10	2		1
1	1	2	2	1	1	5	10	15	2		2

CoMorb	Fangmark	Bitesite	vomit	Locswell	Pain	Cellu	Necfas	coag	Locbleed	Sysbleed	bleedtyp	hemturia
0	1	4	2	1	1	1	2	1	1	2		2
9,10	1	4	2	1	1	1	2	1	1	2		2
0	2	3	2	1	1	1	2	1	1	1		1
0	1	3	2	2	2	2	2	2	2	2		2
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0	2	3	2	1	1	2	2	2	2	2		2
0	1	3	2	1	1	1	2	1	2	1		1
0	1	4	1	1	1	1	2	1	1	2		2
0	2	3	1	1	1	1	2	2	2	2		2
0	1	1	2	1	1	1	2	1	1	1	4	2
0	2	3	2	1	1	1	2	1	1	1		2
0	1	4	1	1	1	1	2	1	1	2		2
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0	1	4	2	1	1	2	2	1	1	1		1
0	1	4	2	1	1	1	2	1	1	1	7	1
0	1	3	1	1	1	1	2	1	1	1	6	1
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0	2	4	1	1	1	2	2	1	1	2		2
0	1	3	2	1	1	1	2	1	1	2		2
0	2	3	2	1	1	1	2	1	2	1	7	2
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0	2	7	2	2	2	2	2	2	2	2		2
0	1	4	1	2	1	2	2	2	2	2		2
0	1	4	2	1	1	1	2	1	1	2		2
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0	1	4	2	2	2	2	2	2	2	2		2
2	1	3	1	1	1	1	2	1	1	1	4	2
0	1	3	1	1	1	1	1	2	2	2		2
0	2	7	2	2	2	2	2	2	2	2		2
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0	1	2	1	1	1	1	2	2	2	2		2
0	1	4	1	1	1	1	2	1	1	1		1
0	1	5	1	1	1	1	1	1	1	1	7	2
0	1	3	1	1	1	1	1	1	1	2		2
0	1	1	1	1	1	1	1	1	1	2		2
1	1	3	2	1	1	1	2	1	1	1		1
0	1	3	1	1	1	1	2	1	1	2		2
1	1	3	1	1	1	1	2	1	1	2		2
2	1	3	2	1	1	1	1	1	1	1	4	1
0	1	4	2	1	1	1	2	1	1	2		2
0	1	6	1	2	2	2	2	2	2	2		2
0	1	4	2	1	1	2	2	2	2	2		2
0	2	4	2	1	1	1	2	2	2	2		2
0	1	2	2	1	1	1	1	1	1	2		2
0	1	2	2	1	1	1	2	1	1	2		2
0	1	4	2	2	1	2	2	1	2	1		1
0	1	4	2	1	1	1	2	1	1	2		2
0	1	2	1	1	1	1	2	1	1	1	4	1
0	1	4	1	1	1	2	2	2	2	2		2

0	2	3	2	2	2	2	2	2	2	2		2
0	1	3	1	1	1	2	2	2	2	2		2
0	1	3	2	1	1	1	2	1	1	2		2
0	1	4	1	2	2	2	2	2	2	2		2
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0	1	3	1	1	1	1	2	1	1	2		2
0	1	4	1	1	1	1	1	1	1	2		2
0	2	3	1	1	1	1	1	1	1	2		2
0	1	1	2	1	1	1	2	2	2	2		2
0	1	3	1	1	1	1	2	1	2	1		2
0	1	1	1	1	1	1	2	1	1	1	4	2
0	1	1	1	1	1	1	2	1	1	1	4	2
0	1	3	1	1	1	1	2	2	2	2		2
0	1	4	1	1	1	1	2	1	1	1	4	2
0	1	4	1	1	1	1	2	1	1	1	6	1
0	2	4	1	1	1	1	2	1	1	1		1
0	1	4	2	1	1	1	2	1	1	1		1
0	1	4	2	1	1	1	2	2	2	2		2
0	1	4	1	1	1	1	2	1	1	2		2
0	1	3	1	1	1	1	2	1	1	1		1

epistax	gumbleed	Compsyn	Neurotox	ptosis	diplopia	pdxresp	Venti	Ventdays	Renfail	dialysis	blodtran
2	2	2	1	1	2	2	2		2	2	2
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2	2	2	1	1	1	2	2		2	2	2
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2	1	2	1	1	1	2	2		1	1	1
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2	2	2	1	1	2	1	1	5	1	1	2
2	2	2	1	1	2	2	2		1	2	2
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2	2	1	2	2	2	2	1	5	1	1	1
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2	2	1	1	1	2	1	2		2	2	2
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1	2	2	1	1	1	2	2		1	2	2
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2	2	2	1	1	1	1	1	2	1	2	2
2	2	1,abdo	2	2	2	2	1	10	1	1	1
2	2	2	1	2	2	1	1	2	1	2	2
2	2	1	2	2	2	2	2		2	2	2
2	2	2	1	2	1	2	2		2	2	2
2	2	2	1	1	1	2	2		1	2	2
2	2	2	2	2	2	2	2		2	2	2
2	2	2	1	2	2	1	2		1	2	2
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2	2	2	1	1	1	2	2		2	2	2
2	2	2	1	1	2	2	2		2	2	2
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2	2	2	1	1	1	2	2		1	2	2
2	2	2	1	1	2	1	2		2	2	2
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2	2	2	1	2	2	1	2		1	2	2
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2	2	2	1	2	2	1	1	2	1	1	1
2	2	2	2	2	2	2	2		2	2	2
1	2	2	1	1	1	2	2		2	2	2
2	2	2	1	1	1	2	2		2	2	2
2	2	2	1	1	1	2	2		1	2	2
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2	2	2	1	2	1	2	2		1	2	2
2	2	2	1	1	1	2	2		1	1	2
2	2	2	1	1	2	2	2		1	2	2
2	2	2	1	1	1	2	2		1	2	2
2	2	2	2	2	2	2	2		2	2	2
2	2	2	1	1	1	1	1	7	1	1	1

No of units transfused	envtype	Outcome	Antbio	tyantbio	GCS	SPO2	HR	SBP	DBP	Tachyp	GRBS	CO2RETEN	ABG
	6	1	1	1	15	95	115	110	70	1	130	2	1
	6	1	1	1	15	90	64	110	60	1	112	2	1
	3	1	1	1	15	95	90	110	60	1	244	2	2
	7	1	1	1	15	98	110	110	70	1	145	2	2
	5	1	1	1	15	98	66	110	70	2	130	2	1
	2	1	1	3	15	96	68	110	70	1	92	2	1
3ffps and 5	7	1	1	1	15	98	110	110	70	1		2	2

cryos													
	7	1	1	1	15	93	74	110	80	1	127	2	2
	7	1	1	4	3	98	160	170	110	1	249	2	2
	7	1	1	1	15	99	78	140	90	1	168	2	1
3ffps and 5 cryos	7	1	1	1	15	100	106	110	70	1	445	2	2
	5	1	1	1	15	90	102	92	66	1	180	2	2
3ffps and 6 cryos 8 plts	3	2	1	4	15	98	116	110	80	1	230	2	2
	3	1	1	1	15	98	166	170	100	1	523	2	2
	2	1	1	1	15	100	120	120	80	1	300	2	1
	3	1	2		15	100	84	120	80	2		2	1
4 ffps and 6 cryos	7	1	1	4	15	97	66	94	60	1	190	2	2
6 ffps 8 cryos 2 prcs	7	1	1	4	15	72	108	150	100	1	153	1	1
	7	1	1	1	15	98	72	140	90	1	281	2	1
	6	1	1	1	15	100	82	130	90	2	167	2	1
	7	1	1	1	15	97	108	90	50	2	160	1	5
6ffps 4plts	7	1	1	4	8	100	86	140	90	1	260	2	2
	5	1	1	1	15	100	82	140	80	2	140	2	1
	3	1	1	1	15	99	72	100	60	2	110	2	1
	4	1	2		9	80	80	170	90	1	207	1	3
	2	1	2		15	100	82	90	70	2	100	2	1
	7	1	1	1	15	86	122	120	70	1	81	2	2
4 plts	7	1	1	4	12	45	118	100	60	1	146	1	5
	1	1	2		15	100	64	110	70	2	120	2	1
4FFPS 2PRCS	7	1	1	1	15	70	142	150	90	1	167	2	1
	5	1	1	1	15	99	98	110	60	1	147	2	1
	4	1	1	1	9t	90	112	100	60	2	103	2	1
	6	1	1	1	15	100	142	100	60	1	108	2	1
	2	1	1	1	15	94	90	110	90	1	94	2	1
	7	1	1	1	8	90	60	140	80	1	122	2	2
8plts 7ffp 2prc	7	2	1	4	8	75	160	80	40	1	38	1	5
	7	1	1	4	15	98	84	100	60	1	100	2	2
	2	1	1	1	15	96	106	140	80	1	107	2	1
	6	1	1	1	15	95	98	120	60	2	162	2	1
	7	1	1	1	12	90	128	100	60	1	107	2	1
	3	1	1	3	15	92	144	80	60	1	390	2	1
	7	2	1	5	15	90	112	120	70	1	148	2	2
	6	1	1	1	15	98	78	120	70	2	83	2	2
	4	1	2		15	95	92	110	60	2	136	2	1
	6	1	2		15	96	90	110	80	1	140	2	1
	5	1	1	1	15	98	120	120	76	1	140	2	1
	2	1	1	2	15	98	106	120	70	1	78	2	2
	3	1	1	1	15	98	98	120	80	2	97	2	2
	3	3	1	1	15	94	112	80	50	1	182	2	1
	7	1	1	1	15	93	112	90	70	1	241	2	1
	6	1	1	1	15	96	130	110	70	1	137	2	4
	3	1	1	1	15	100	96	110	60	1	130	2	1
	1	1	2		15	98	78	140	90	2	153	2	1
	2	1	2		15	96	84	130	90	2		2	1
	6	1	2		15	94	82	90	60	1	166	2	2
	7	1	1	1	15	95	96	130	90	1	222	2	2
	5	1	1	1	15	96	96	90	60	2	263	2	1
	7	1	1	3	15	98	82	120	80	2	123	2	2
4 ffps	7	1	1	4	15	97	86	110	80	1		2	2
	7	1	1	1	15	92	122	170	80	1	422	2	1
	3	1	1	1	15	98	118	90	60	1	169	2	1

	6	1	1	1	15	92	100	100	70	1	88	2	2
	6	1	1	3	15	98	74	100	70	2	165	2	1
	7	1	1	1	15	96	110	100	70	2	146	2	2
	6	1	1	1	15	95	112	90	60	1	125	2	1
	6	1	1	1	15	96	84	90	60	2	194	2	1
	7	1	1	1	15	96	66	120	90	1	143	2	1
	7	1	1	1	15	99	100	180	100	2	143	2	2
	7	1	1	2	15	91	74	150	100	1	195	2	1
	7	1	1	1	15	98	92	90	60	2	171	2	2
	3	1	1	1	15	96	90	120	80	1	126	2	1
	7	1	1	5	15	86	142	90	60	1		1	5

Hb	Anemia	TC	highTC	Plts	lowplts	HUS	CXR	ECG	Icterus	TB	Alb	SGOT	SGPT	heptitis	Rhabdo	CPK
15.8	2	9000	2	253000	2	2	1	2	2	1	4.5	36	10	2	1	275
16.4	2	2500	2	144000	2	1	1	1	1	3.6	3.6	89	19	2	1	315
12.5	2	18500	1	152000	2	2	1	1	2						2	
15.4	2	20600	1	190000	2	1	1	2	2						1	681
15.3	2	13500	1	178000	2	2	1	1	2							
12.7	2	7800	2	23900	1	2	1	1	2						2	85
10.7	1	24900	1	108000	2	1	1	1	1	4.2	4.2	134	29	1	1	913
6.6	1	7400	2	151000	2	1	1	1	2	0.5	2.7	52	12	2	1	1404
12.9	2	34900	1	25000	1	1	1	2	2	0.7	1.6	29	28	2	1	11374
13.8	2	10500	2	294000	2	2	1	1	2						1	2923
14.4	2	25600	1	66000	1	1	1	2	2	1.9	3.6	142	36	1	1	2089
15.8	2	9000	2	253000	2	2	1	2	2	1	4.5	36	10	2	1	275
8.1	1	21700	1	50000	1	1	1	2	2						1	7498
14	2	20400	1	251000	2	2	1	2	2	1.6	3.9	58	20	2	2	95
13.9	2	7300	2	256000	2	2	1	2	2	0.4	4.5	15	8	2	2	
12.9	2	14900	1	177000	2	2	1	1	2	0.5	4.5	17	9	2	2	155
8.1	1	16700	2	50000	1	1	1	2	2	0.7	4.3	35	13	2	1	434
12.4	2	21400	1	44000	1	1	2	2	1	11	3.6	238	37	2	1	431
13.3	2	10000	2	61000	1	1	1	1	2						2	116
13.4	2	12000	1	175000	2	2	1	1	2						1	2214
13.7	2	53500	1	263000	2	1	2	2	1	2.2	3	229	53	1	1	6448
7.9	1	37200	1	11000	1	1	1	2	1	3.8	4.3	960	89	1	1	10114
11.6	2	22000	1	291000	2	2	1	2	2						1	1817
15.	2	2600	1	10200	1	2	1	1	2						1	2108

7		0		0												
12.1	1	17700	1	333000	2	2	1	1	2							
14.1	2	6900	2	178000	2	2	1	1	2	0.9	3.5	34	15	2		
10	1	19700	1	74000	1	1	1	2	1	2.1	3	108	22	1	1	853
10	1	13400	1	15000	1	1	2	2	1	3.6	3.3	244	71	1	1	7761
14.7	2	5900	2	241000	2	2	1	1	2	0.5	4.2	26	16	2		
11.5	1	41900	1	516000	2	1	1	2	1	2.8	3.8	137	35	2	1	2169
9.1	1	24700	1	375000	2	2	1	1	2	0.4	4.1	22	10	2	2	146
13	2	10120	2	284000	2	2	1	2	2	0.4	3.4	41	23	2	2	138
12.7	2	8830	2	75000	1	1	1	1	2	1.2	3.6	38	16	2	1	220
13.7	2	8500	2	208000	2	2	1	1	2	0.5	4.2	20	12	2	1	245
10	1	41150	1	32000	1	1	1	1	1	7.7	2.8	250	29	1	1	11380
6.1	1	21600	1	11000	1	1	1	2	1	14	2.4	103	69	1	1	5142
14.7	2	38800	1	32000	1	1	1	1	2	1.4	3.1	1120	186	1	1	40340
12.9	2	16000	1	269000	2	2	1	1	2						1	380
14.2	2	16600	1	196000	2	2	1	1	2						1	257
16	2	21200	1	145000	1	1	1	1	1	3	2.8	118	40	1	1	5502
16.1	2	4100	2	143000	1	2	1	1	2	1.8	3.7	23	10	2	1	2189
11.1	1	12100	1	93000	1	1	1	1	1	7.9	3.7	215	99	1	1	11506
10.6	2															
13.3	2	13800	1	262000	2	2	1	1	2	0.3	4.7	15	6	2		
14.1	2	7200	2	213000	2	2	1	2	2			53	14	2	1	1433
11.5	2	21000	1	291000	2	2	1	2	2	0.4	3.4	38	19	1	1	269
15	2	8700	2	155000	2	2	1	2	2						1	880
11.6	2	13300	1	68000	1	1	1	2	2	1.3	3.1	63	34	2	1	1498
15.2	2	19900	1	260000	2	2	1	1	2							
13.7	2	26300	1	223000	2	2	1	2	2	1.1	4.1	23	11	2	2	162
13	2	22060	1	251000	2	2	1	2	2	0.4	3.7	27	12	2	2	129
9.4	1	15200	1	23700	2	2	1	1	2	0.5	3.6	10	10	2	1	550
12	2	9200	2	280000	2	2	1	1	2					2		
15.6	2	5900	2	1,61,000	2	2	1	1	2	0.7	4.5	23	16	2		
15.6	2	11700	2	77000	1	1	1	1	2	1.7	3.5	55	14	2	2	178
13.3	2	20100	1	129000	2	1	1	1	2						1	541
11	1	27200	1	386000	2	2	1	2	2						1	704
14.5	2	18300	1	60000	1	1	1	1	1						1	674

14.2	2	14100	1	188000	2	1	1	1	2						1	2224
13.8	2	22700	1	189000	2	1	1	1	1	4.9	3.1	222	36	2	1	5753
17.7	2	17500	1	336000	2	2	1	1	2						2	186
11.5	2	6700	2	168000	2	2	1	1	1	2.6	3.1	61	24	2		
12.9	2	21000	1	241000	2	2	1	1	2	1.7	4.1	63	38	2		
15.9	2	23100	1	99000	1	1	1	1	1	3.5	3.2	110	9		1	3427
17	2	13700	1	263000	2	2	1	1							1	9495
14.3	2	17600	1	177000	2	2	1	1	1	2.7	4.6	80	35	2		
6.7	1	21500	1	100000	1	1	2	1	1						1	688
9.1	1	20800	1	189000	2	1	2	1	1	14	3.7	75	28	2	1	3985
11.1	2	26900	1	257000	2	2	1	1	2						1	2791
14.6	2	15300	1	67000	1	1	1	1	2						1	1600
13	2	11700	2	99000	1	2	1	1	2	1.4	3.9	40	12	2		
7.2	1	32600	1	30000	1	1	2	2	1	8.6	3	470	55	2	1	7327

LDH	Creat	Neostig	MRCGrade	Urincolr	Urea	Na	K^+	Urinalys	Fibval	lowfib	Timenorm	SSscore	Severity	sevcode
	1.24	2	5	2	31	142	4.5	4			2	4	moderate	1
	1.25	2	5	2	31	134	4.3	4			2	9	high	2
	1.73	2	5	2	51	141	3.8	4			2	8	high	2
931	2.8	1	4	2	69	139	2.8	2			2	4	moderate	1
	1.2	1	5	1	33	139	3.6	1			2	8	high	2
	0.96	2	5	1	43	138	2.9	1			1	3	mild	1
2459	9.43	2	5	2	92	139	3.9	4	22.6	1	2	8	high	2
	7.47	2	5	2	88	141	4	4			1	8	high	2
2356	8.2	1	5	2	155	146	5	4			1	9	high	2
	3.33	2	5	2	60	146	3.2	4			2	11	high	2
3680	9.5	2	5	2	82	134	4.9				1	9	high	2
	1.24	2	5	2	31	142	4.5	4			2	5	moderate	1
3098	6.74	2	5	2		117	5.5		235	2	1	8	high	2
1822	2.17	2	5	2	41	129	5.3	4			2	9	high	2
	1.05	2	5	1	19	137	4.1				1	3	mild	1
	1.49	2	5	2	28			2			2	6	moderate	1

763	1.9	2	5	2	52	138	4.2	4	118	1	4	9	high	2
514	3.9	2	5	2	90	132	4.3	4	127	1	1	10	high	2
233	2.3	2	5	1	25	142	3.5	3	0	1	4	9	high	2
	0.72	2	5	2	23	138	3.1	4			2	5	moderate	1
875	2.75	2	5	2	117	131	3.6	4			3	9	high	2
2300	2.11	2	5	2	100	139	5.4	4	265	2	3	9	high	2
	0.5	1	5	2	24	137	4	4			2	3	mild	1
712	1.32	2	5	1	51	146	4	3			3	10	high	2
	1.01	1	0	1	31	133	3.7	1			1	9	high	2
	0.73	2	5	1	32	136	3.9	1			1	3	mild	1
1263	4.58	2	5	2	111	140	4.4	4	406	2	2	9	high	2
1394	7.08	2	4	2	129	129	3.4	4	560	2	2	9	high	2
	0.97	2	5	1	21	139	3.6	1			1	3	mild	1
	4.78	2	5	2	88	143	5	4			3	5	moderate	1
	0.53	2	5	1	30	132	3.1	4			1	6	moderate	1
	0.5	2	0	1	10	133	3.6	1			1	6	moderate	1
	1.87	2	1	2	39	139	3	4	480	2	2	8	high	2
	0.73	2	5	1	38	133	5	1			1	2	mild	1
	1.4	1	3	2	85	147	3.7	4	320	2	3	8	high	2
2166	5.7	1	5	2	205	139	4.5	4	354	2	3	9	high	2
3248	0.74	1	3	2	57	133	4.3	4	630	2	3	10	high	2
	0.73	2	5	1	23	143	3.4	1			1	4	moderate	1
	1.17	2	5	1	35	138	3.5	2			2	9	high	2
1853	1,14	1	3	2	23	145	3.5	4	53	1	3	5	moderate	1
	0.9	2	5	2	30	137	3.3	4			2	6	moderate	1
5248	6.34	2	0	2	260	142	5	4	471	2	4	8	high	2
	0.91	2	5	1	19	139	4.2	1			2	3	mild	1
	0.71	1	4	1	23	142	3.5	2			1	5	moderate	1
	0.89	1	4	2	34	139	3.2	4			2	5	moderate	1
	0.72	2	4	1	24	134	3.3	4			1	3	mild	1
	0.99	2	5	1	23	137	4.2	1			1	4	moderate	1
756	10.2	2	5	2	141	136	4.2	4			1	6	moderate	1
	1.24	2	5	1	37	136	3.7	1			1	3	mild	1
	1.3	2	5	1	26	140	3.7	1			2	2	mild	1
459	0.5	2	5	1	15	13	3.6	4			1	5	moderat	1

						4							e	
	0.8	2	5	1		133	4	1	371	2	2	5	moderate	1
	0.99	2	5	1	20			2			1	2	mild	1
	0.91	2	5	1	17	140	3.2	1			1	3	mild	1
	1.5	2	5	1	44	139	3.4	2			2	4	moderate	1
824	1.89	2	5	1	41	142	4.1				3	4	moderate	1
	0.81	2	5	1		141	3.7	1			1	8	high	2
637	12.1	2	5	2	208	143	4.5	4			1	10	high	2
2634	1.27	2	5	2		135	4,2	4			2	7	moderate	1
4499	3.55	2	5	2	119	128	4.3	4			2	8	high	2
	1.45	2	5	1	36	136	3.7	1			2	6	moderate	1
	0.8	1	5	2	17	141	3.3	4			3	10	high	2
	1.13	2	5	1	36	140	4	1			3	7	moderate	1
1524	3.7	2	5	2	35	137	3.5	4			3	8	high	2
	1.22	2	5	1	36	132	3.3	4			1	3	mild	1
	1.39	2	5	2	31	144	4.3	4			2	6	moderate	1
1152	8.56	2	5	2	113	140	4.7	4			1	9	high	2
224	7.36	2	5	2	153	141	4.4	4	225	2	3	7	moderate	1
	0.91	2	5	1		136	3.5	1			1	5	moderate	1
	1.76	2	5	2	39	133	3.6	4			1	4	moderate	1
	1.28	2	5	2	29	136	3.9	2			2	5	moderate	1
3493	11.1	2	3	2	230	140	4.5	4	447	2	2	11	high	2

WBCT	PT	Ptvalue	INR	aptt	Apttval	TEG/Rotem	CT(324-565)	CFT(112-224)	α(50-68)	MCF(55-66)	ML(0-15)
2	2	20.8	1.87	1	23.7	1	293	157	61	49	4
2	2	67.8	6.28	1	35.2	2	981	0	7	15	
2	2	21.8	1.96	1	28.6	2	391	780	28	30	1
2	2	19.3	1.74	1	25.1	2	410	647	38	34	2
2	2	28.5	2.54	2	40.1	2	272	199	54	50	7
1	1	12	1.1	1	25	1	305	103	70	59	19
2	2	21.8	1.96	1	31.4	2	2530			5	1
1	1	10.9	1	1	25	2	860	441	33	39	10
1	1	11.8	1.08	1	35.1	2	550	411	37	49	10
2	2	41.4	3.65	1	34.8	2	349	444	38	41	0
1	1	11.9	1.09	1	25	2	365	295	43	45	
1	2	20.8	1.87	1	23.7	2	171	298	44	48	12
1	1	13.7	1.14	1	35.4	2	470	232	49	43	1
2	2	25.3	2.26	1	30	2	2357				
1	1	10.9	1	1	24.6	1	217	88	72	64	6
2	1	11.8	1	1	24.2	1	315	129	65	52	11
2	2	130	10	2	200	2	5395				

1	1	12.4	1.1	1	24.7	2	401	494	30	37	1
1	1	11.4	1.04	1	27.9	2	2305	0	0	4	N\A
2	2	16.5	1.51	1	23	1	235	267	54	57	15
1	2	15.1	1.38	1	28	1	283	119	67	59	2
2	2	42.7	3.58	1	28.3	2	389	115	67	48	7
1	1	13	1.2	1	24	1	304	122	66	57	9
2	2	31.4	2.68	1	35.5	2	652	1424	22	25	1
1	1	11.6	1.06	1	26.3	1	256	102	71	71	6
1	1	11.1	1.02	1	31	1	223	80	74	59	10
2	1	12.4	1.2	1	31	2	753	343	41	41	7
2	2	15.6	1.42	1	36.4	2	849	632	25	34	5
1	1	11.9	1.08	1	25	1	283	204	58	64	3
2	2	47.2	4.35	2	70	1	280	81	74	70	6
1	1	12.5	1.14	1	27	1	191	102	72	75	7
1	1	12.5	1.14	1	26.9	1	230	104	69	59	12
1	2	18.8	1.72	2	43.7	2	738	388	35	41	9
1	1	10.8	1	1	25	1	184			9	
2	2	19.8	1.81	2	114.4	2	2284		11	8	40
1	2	27.3	2.5	2	44.1	2	582	356	37	35	
2	2	28	2.57	2	36.8	2	1244	556	28	35	
1	1	11	1	1	24	2	979	2518	7	35	
1	1	13	1.18	2	68	2	1209	1431		40	
2	2	31.9	2.93	1	34.4	2	1324	1864	57	10	14
1	1	13.5	1.23	1	25.4	2	768	2900	9	31	
2	2	18.9	1.73	1	37	2	397	404	39	52	3
2	2	23	2.14	1	25	2	1192			17	
1	1	11.1	1.01	1	25	1	296	91	72	63	8
2	1	12	1.1	2	180	1	199	96	71	60	
1	1	12.5	1.14	1	26.2	1	418	142	63	53	
1	1	10.9	1	1	24	1		not done			

2	1	11.6	1.06	1	24.8
1	1	12.5	1.1	1	34
2	2	14.4	1.41	1	30.6
2	1	11.4	1.04	1	24
1	1	9.7	0.88	1	27
1	1	10.2	0.94	1	28.9
1	1	11.3	1.04	1	31
2	2	26.4	2.36	2	107.3
1	2	18.5	1.67	1	24
1	1	12.5	1.14	1	24
1	2	14.2	1.29	1	29.1
2	2	49.2	4.31	2	120
2	2	17.9	1.59	1	28.1
2	2	28.7	2.56	1	31.1
2	2	120	10	2	180
	2	38.1	3.37	1	36.4
2	2	18.3	1.65	1	25.1
1	2	24	2.15	1	25.3
2	2	18.9	1.71	1	28.2
1	1	13	1.19	1	26.3
1	2	14.4	1.31	1	27.7
1	2	14.4	1.31	1	32.8
2	2	21.3	1.92	1	29.5
2	2	57	4.98	1	24.1
2	2	22.9	2.05	2	46.7

R(3-8)	K(1-3)	Angle(55-78)	MA(51-69)	Ly30(0-8)
4.3	2.3	56.3	52.9	0.1
32.8	N\A	2.3	9.7	0
5.3	8	36.8	34.8	0
5.8	7.3	35	38.3	0
7.1	8.3	25.1	41.9	0
7.5	2.5	55.6	60.1	0
33.8	N\A	1.6	2.4	0
11.5	8.9	23.6	43.4	0
12.9	6.8	26.9	50.8	0
6	9.3	18.7	41.7	0
6.9	4	39	41.8	0
3.6	2.3	62.7	52.9	0
11.8	5.3	33.6	44.7	0
26.9	N\A	1.7	2.2	0
3.1	1.2	74.6	61.7	0.3
4.8	2.2	58.8	56.3	0
NOT DONE				
NOT DONE				
195.5	0	0	0	0
7	1.9	59.5	62.3	0.6
3.8	1.7	53.4	64.5	0
7.9	18	28.5	21.2	0
NOT DONE				
NOT DONE				
13.5	5.1	31.6	62.9	0
NOT DONE				
NOT DONE				
17.9	10.6	20.2	34.3	0
NOT DONE				
NOT DONE				
NOT DONE				
NOT DONE				
NOT DONE				
NOT DONE				
NOT DONE				
NOT DONE				
NOT DONE				
NOT DONE				
NOT DONE				
NOT DONE				
NOT DONE				
NOT DONE				
NOT				

DONE				
NOT DONE				
NOT DONE				
3.8	2.5	58.3	54.1	0
7.1	2.7	53.4	59.4	0
6.6	4.7	44.1	56.1	0

SEX

1. MALE
2. FEMALE

Occupation(OCCU)

1. Agriculture
2.Coolie / Casual Labour/service
3. Housewife
4. Office Work / business / Doctor
5. Retired Staff
6. Students
7. Unemployed

age

1.<20
2.21-40
3.41-60
4.>60

ADDRESS (adrs)

1. TN
2. AP
3. Others

TIME OF BITE (TOB)

1. Morning
2. Afternoon
3. evening
4. Night

TIME ELAPSED SINCE BITE (TESC)

1. < 6 hours
2. 6-12 hours
3.12-24 hours
4. > 24 hours

MODE OF TRANSPORT (modtrans)

1. Foot
2. Motorcycle
3. Rickshaw/auto
4. Four wheeler
5. Ambulance

SNAKE IDENTIFIED (snidenyn)

1. YES
2. NO

SNAKE TYPE (sntype)

1. Russel's viper
2. Saw scaled viper
3. Indian cobra
4. Krait
5. not identified

SNAKE BROUGHT WITH PATIENT - snbring

1. yes
2. no

ENVIRONMENT SETTING (envsetng)

1. outdoor/fields
2. house/indoor
3. water bodies
4. others

FIRST AID/LOCAL MEASURES GIVEN ? - FIRSTAID

1. Yes
2. No

TYPE OF FIRST AID/ LOCAL MEASURES - AIDTYPE

1. Tourniquet
2. multiple incisions
3. herbal/native medicine
4. none
5. local anaesthetic

TETANUS TOXOID - TETTOX

1. yes
2. no

PRIOR ASV

1. Yes
2. No

ASV Hypersensitivity ? - ASVhyper

1. Yes
2. No

Type of ASV hypersensitivity ? - tyasvhs

1. Mild
2. Severe

CO MORBIDITIES - comorb

1. DM
2. HTN
3. IHD/CAD
4. CKD
5. CLD
6. Prior antiplatelet / anticoagulant therapy
7. Known bleeding disorder
8. Malignancy
9. smoking
10.alchohol consumption
11. others

FANG MARKS

1. Yes
2. No

SITE OF BITE - BITESITE

1. Right upper limb
2. Left upper limb
3. Right lower limb
4. Left lower limb
5. Trunk
6. Face
7. Other areas

Local edema/swelling - Locswell

1. Yes
2. No

PAIN

1. Yes
2. No

CELLULITIS - cellu

1. Yes
2. No

GANGRENE

1. Yes
2. No

LOCAL BLEEDING - locbleed

1. Yes
2. No

Systemic bleeding/ Compartment syndrome

1. Yes
2. No

TYPE OF SYSTEMIC BLEED - bleedtyp

1. Bleeding Gums
2. Epistaxis/Hemoptysis
3. Hematuria
4. Hemetemesis
5. Bleed PR/ Malena
6. IV site ooze
7. Internal bleed eg. Intra cranial / Intra abdominal
8. Others

Neurotoxicity - neurotox

1. yes
2.no

What neurologic manifestation ? - nutoxTyp

1. Ptosis/drooping eyelids
2. Opthalmoplegia / Diplopia
3. Breathing difficulty/ paradoxical resp
4. Severe muscular weakness
5. Other Cranial nerve palsies
6. Other manifestations ?

VENTILATION - VENTI////// RENAL FAILURE - renfail
DIALYSIS/////// BLOOD TRANSFUSION - blodtran

1. yes
2. no

NO OF VENTILATION DAYS - VENTDAYS
TYPE OF SNAKE ENVENOMATION - envtype

1.No envenomation
2.Local swelling only
3.Haemotoxicity with / without local swelling
4.Neurotoxicity only
5. Neurotoxicity with Local swelling
6.Haemotoxicity + Neurotoxicity with / without local swelling
7.Haemotoxicity + Neurotoxicity +renal failure with local swelling
8.Neurotoxicity + myoglobinuria

OUTCOME

1. completely recovered
2. Died
3. Discharged against medical advice
4. Referred to higher/other centres

type of Antibiotic - TYANTBIO

1. Augmentin
2. Benzyl penicillin
3.cloxacillin
4. piptaz
5.meropenem
6.colistin

20 MIN WBCT

1. Normal
2. Prolonged

URINE COLOUR - urincolr

1. Clear
2. Brown/red

ABG

1. Normal
2. Metabolic acidosis
3. Respiratory acidosis
4. Respiratory alkalosis
5. Metabolic Acidosis + Respiratory Acidosis

URINE ROUTINE

1. normal
2. hematuria
3. proteinuria
4. hematuria + proteinuria

SNAKE BITE SEVERITY

1. Mild to Moderate severity
2. Severe envenomation

TIMENORM- time to normal bleeding tests

1. <12 hours
2. 12-24 hours
3. 24- 48 hours
4. 48 - 72 hours
5. >72 hours